

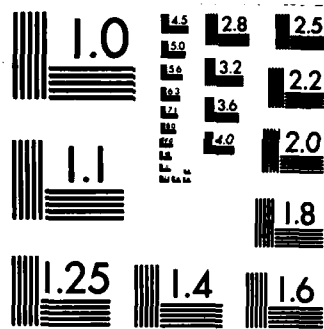
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# DEPARTMENT OF CLINICAL INVESTIGATION

## ANNUAL RESEARCH PROGRESS REPORT

FISCAL YEAR 1984



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ANNUAL PROGRESS REPORT

30 September 1984

DEPARTMENT OF CLINICAL INVESTIGATION

MADIGAN ARMY MEDICAL CENTER

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| 18. SUPPLEMENTARY NOTES<br>The findings in this report are not to be construed as an official Department of the Army position unless so designated by other authorized documents.   |                                      |  |
| 19. KEY WORDS (Continue on reverse side if necessary and identify by block number)<br>Unit summary; research protocols (objective, method, progress, status); publications; presentations.  |                                      |  |
| 20. ABSTRACT (Continue on reverse side if necessary and identify by block number)<br>Subject report identifies those individuals who are conducting investigative protocols at Madigan Army Medical Center. An abstract of each protocol giving abbreviated technical objectives, methods, and progress is presented. The protocols are in the following fields: clinical investigation; emergency medicine; pathology; radiology; nursing; statistics and gynecology; pediatrics; psychology; surgery; nutrition care; preventive medicine; children's cancer; oncology. |                                      |  |

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# ANNUAL RESEARCH PROGRESS REPORT

FISCAL YEAR 1984

DEPARTMENT OF CLINICAL INVESTIGATION  
MADIGAN ARMY MEDICAL CENTER  
TACOMA, WASHINGTON 98431-5454

In conducting the research described in this report, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care" as promulgated by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences National Research Council, and the Guiding Principles in the Care and Use of Animals (Appendix I) approved by the Council of the American Physiological Society. The investigators follow the recommendations from the Declaration of Helsinki (Appendix II) in the performance of investigations involving human subjects.

## ACKNOWLEDGEMENTS

I would like to take this opportunity to thank Nancy Whitten for the effort which is obvious in the compilation of this publication which is ever increasing in size and Genie Hough for clerical assistance.

## FORWARD

In order to perform as a medical center, three missions must be accomplished. They include service to our patient population, research into problems affecting and pertinent to that population, and finally teaching at all levels of medical care providers. It is important in accomplishing these missions effectively that they not be approached as separate entities but as part of a single goal to develop and maintain an excellent medical center. As can be seen by the contribution from all portions of the hospital in this annual report of 250 protocols and some 63 publications, either published or in press this year, with an additional 20 having been submitted and waiting review, everyone is pulling together in the area of research to accomplish the overall goal of making Madigan an outstanding medical center. It is also apparent that accomplishing this goal has required additional effort from all persons involved because an increased productivity in the investigative arena has been accomplished while manpower resources in all parts of the hospital have at best been stable. The future of the medical center appears even brighter this year since it is obvious that we continue to have staff in all departments who are interested and accomplished in their abilities to be at the cutting edge of medical care which is accomplished through research. We have seen ground-breaking occur for a new Madigan Army Medical Center.

Research protocols described in this report were conducted under the provisions of AR 40-38, Clinical Investigation Program; AR 7025, Use of Volunteers as Subjects of Research, and MAMC Supplement 1 to HSC Regulation 40-23, Medical Services Clinical Investigation Program.

The staff of Department of Clinical Investigation would like to express our appreciation for the support derived from the hospital during the past year, which made these investigative procedures possible. I would like to thank Nancy Whitten for her effort in compiling and preparing this report. The staff at Department of Clinical Investigation most of all wishes to thank the personnel in the hospital for their interest and efforts in accomplishing a most important mission.

# UNIT SUMMARY FY 84

## 1. Objective

To provide the facilities and environment to stimulate an interest in clinical and basic investigations within Madigan Army Medical Center.

## 2. Technical Approach

| <u>DESCRIPTION</u>   | <u>MANPOWER</u> | <u>RANK</u> | <u>MOS</u> |
|--|-----------------|-------------|------------|
| Chief (Aug/Sep 84)<br>PLYMATE, Stephen R., M.D., COL, MC                               |                 | O6          | 61C9A      |
| Chief (Oct 83 - Aug 84)<br>FARISS, Bruce L., M.D., COL, MC                             |                 | O6          | 61C9A      |
| C, Surg & Animal Care Svc<br>(Jul 84 - Sep 84)<br>YARBROUGH, Leslie, D.V.M., MAJ, VC   |                 | O4          | 64C9B      |
| C, Surg & Animal Care Svc<br>(Oct 83 - Jul 84)<br>LIEBENBERG, Stanley, D.V.M., MAJ, VC |                 | O4          | 64C9B      |
| C, Microbiology Svc<br>HIGBEE, James W., Ph.D., MAJ, MSC                               |                 | O5          | 68A9B      |
| C, Biochemistry Svc<br>LITTLE, James S., Ph.D., MAJ, MSC                               |                 | O4          | 68C9C      |
| C, Physiology Svc<br>FRIEDL, Karl E., Ph.D, CPT, MSC                                   |                 | O3          | 68J9B      |
| NCOIC (Sep 84)<br>HAYES, James E.  |                 | E6          | 91T3R      |
| NCOIC (Sep 83 - Apr 84)<br>MCDONALD, Karl O.   |                 | E5          | 91T2R      |
| Med Lab Spec<br>JONES, Richard E.  |                 | E7          | 92B4R      |
| OR Tech (Oct 83 - Feb 84)<br>SATTEFIELD, Thomas  |                 | E6          | 91D2R      |
| OR Tech (Mar 84 - Sep 84)<br>WORRELL, Carleen  |                 | E4          | 91D1T      |
| Vet Animal Spec<br>MORMILE, Andrea K.  |                 | E5          | 91T2R      |

| <u>DESCRIPTION</u>                   | <u>RANK</u> | <u>MOS</u> |
|--------------------------------------|-------------|------------|
| Vet Animal Spec<br>SCUTELLA, John    | E4          | 91T1R      |
| Vet Animal Spec<br>SCHUPANITZ, Bruce | E5          | 91T2R      |
| Med Tech<br>GARRISON, Mina J.        | GS9         | 0644       |
| Med Tech<br>KETTLER, Thomas M.       | GS9         | 0644       |
| Med Tech<br>MATEJ, Louis A.          | GS9         | 0644       |
| Edit Asst/Steno<br>WHITTEN, Nancy J. | GS6         | 1087       |
| Sec/Steno<br>HOUGH, Eugenia R.       | GS4         | 0318       |
| Maintenance Worker<br>KAEO, Curtis   | WG7         | 4749       |

|                      | <u>FUNDING</u> |
|----------------------|----------------|
| MEDCASE Equipment    | \$100,302.00   |
| Capital Equipment    | 2,728.00       |
| Civilian Salaries    | 135,838.00     |
| Consumable Supplies  | 91,125.00      |
| Contractual Services | 11,442.00      |
| TDY                  | 6,678.00       |
| TOTAL                | \$348,113.00   |

### 3. Progress

During FY 84 there were 257 active protocols that received administrative and/or technical support during the year. Of these, 143 are presently ongoing; 74 were completed; 29 were terminated, three were transferred to other MEDCEN's, and eight are in a suspended status until further word is received from DA regarding the use of dogs and cats in research

There were 44 publications, 19 papers are in press, and 20 papers have been submitted to journals for possible publication. There were 34 presentations at regional, national or international meetings resulting from these protocols. Two of these presentations were cited by the national news media.

C O M M I T T E E   M E M B E R S

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THE BYRON L. STEGER RESEARCH AWARD

Submissions are judged on their scientific merit, relevance, objectivity of evaluation, interpretation of results, and the potential importance of the subject of the research.

Recipient of this award for 1984:

|                              |  |
|------------------------------|--|
| Peter A. Maningas<br>CPT, MC | Transcutaneous Oxygen Monitoring During<br>Hemorrhagic Shock |
|------------------------------|--|

Other Nominees were:

|                                 |   |
|---------------------------------|---|
| Frederick E. Harlass<br>CPT, MC | Weight Loss Corrects Gonadotropin and<br>Sex Steroid Abnormalities in the Obese<br>Anoulatory Female                                    |
| Michael J. O'Reilly<br>CPT, MC  | Sepsis from Sinusitis in Nasotracheally<br>Intubated Patients: A Diagnostic Dilemma   |
| Merlin R. Robb<br>CPT, MC       | The Use of Oral Folinic Acid in the<br>Prevention of Neutropenia Associated<br>with Standard Trimethoprim-Sulfamethox-<br>azole Therapy |
| William J. Watson<br>CPT, MC    | Outcome of Vaginal Delivery for the<br>Selected Frank Breech Infant at Term   |

PUBLICATIONS.....FY 84

COMPTROLLER'S OFFICE

Publication:

Reeves, R.L. and Thompson, J.W.: A Workshop Paradigm for Constructing the Performance Work Statement. Armed Forces Comptroller, Spring 1984, pp 26-29.

DEPARTMENT OF CLINICAL INVESTIGATION

Publications:

Liebenberg, S.P.: What's Your Diagnosis - Hotfoot. Lab Animal 13(4): 17-18, 1984

Liebenberg, S.P., Fitzpatrick, M.C., and Jones, M.H.: What's Your Diagnosis - Out of Breath. Lab Animal 13:15-16, 84.

Liebenberg, S.P. and Taylor, W.E.: The Carbon Dioxide Laser; Its Use in Pharyngeal Surgery in the Dog. Vet Med 4:497-504, 1984.

Little, J.S.: Biochemical and Cytochemical Localization of Inosine-5'-Diphosphatase in Rat Liver Microsomal Fractions. Biochem J 218: 501-510, 1984

Little, J.S. The Effect of *Streptococcus pneumoniae* Infection on the Binding of Thyroxine to Purified Rat Liver Plasma Membranes. Endocrinology 114:411-17, 1984.

Plymate, S.R.: Treatment of Idiopathic Oligospermia. Fertil Steril 41:163, 1984.

Plymate, S.R., Fariss, B.L., Miles, B., and Matej, L.A.: The Relationship of Testicular Dysfunction and Age to Impotence. J Andrology 5(1): 15, 1984.

Plymate, S.R., Stutz, F.H. and Fariss, B.L.: Relationship Between Sex Hormone Binding Globulin and Estrogen Receptors in Breast Cancer. J Clin Oncology 2(6): 652-54, 1984

Plymate, S.R., Vaughan, G.M., Jackson, R.E., and Fariss, B.L.: Abnormalities in Pituitary Testicular Axis in Severely Ill Men. J Andrology 5(1): 15, 1984.

Accepted for Publication:

Friedl, K.E. and Plymate, S.R.: Effects of Obesity on Reproduction in the Female. Accepted by J Obesity Weight Reg, Nov 83.

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Sweeney, J.K.: Neonatal Hydrotherapy: An Adjunct to Developmental Intervention in an Intensive Care Nursery Setting. Presented to Eastern Regional Neurodevelopmental Therapy Conference, Washington, DC, November 1984.

Weisman, L.E., Fischer, G.W., Pierce, J.R., Hemming, V.G., Marinelli, P., Hunter, K.W., and Golden, S.M.: Intravenous Immunoglobulin Therapy in the Neonate: A Study of Pharmacokinetics and Safety. Presented to the American Academy of Pediatrics, New York, NY, October 1983.

### PREVENTIVE MEDICINE ACTIVITY

Fletcher, D.: Hepatitis B Vaccine --Current Concepts and Strategies. Presented to the Pierce County Medical Society, Tacoma, WA, April 1984.

### DEPARTMENT OF SURGERY

Belville, W.D.: Computerized Tomography in Urologic Oncology. Presented to Northwest Urological Association Meeting, Portland, OR, Dec 1983.

Maughan, D.R. and Liebenberg, S.P.: Calcium Sulfate (Plaster of Paris) as an Alloplastic Implant in Mandible Reconstruction in the Dog. 34th Annual Meeting of the American Association for Laboratory Animal Science, San Antonio, TX, November 1983.

O'Reilly, M.J., Reddick, E.J., Black, W., Carter, P.L., Erhardt, J., Fill, W., Maughn, D., Sado, A., and Klatt, G.R.: Sepsis from Sinusitis in Nasotracheally Intubated Patients. Presented to 70th Annual Meeting of the Northern Pacific Surgery Association, Victoria, BC, Nov 1983.

## PRESENTATIONS - FY 84

### Department of Medicine (Cont)

Knodel, A.R., Covelli, H.D., and O'Reilly, M.: The Role of Mask CPAP in Preventing Post-Operative Atelectasis. Presented to American Thoracic Society Meeting, Miami Beach, FL, May 1984. Abstract Amer Rev Resp Dis 129:A110, 1984.

Redmond, J.P., Spring, D.B., Munderloh, S.H., George, C.B., Monsour, R.P., and Volk, S.A.: Spinal Computed Tomography (CT) Scanning in the Evaluation of Metastatic Disease. Presented to American Society of Clinical Oncology, May 1984.

Redmond, J.P.: Spinal Computed Tomography (CT) Scanning in the Evaluation of Metastatic Disease. Presented to the Pierce County Medical Society, Tacoma, WA, April 1984.

Steudel, W.T.: Variable Angina Threshold in Patients With Coronary Artery Disease. Presented to American Academy of Family Physicians, Miami, FL, October 1983.

Treece, G.L. and Carlin, K.: Lack of Clinical Utility of the Thyroglobulin Antibody Test by Hemagglutination. Presented to the American Thyroid Association, October 1983.

### DEPARTMENT OF OB/GYN

Maslow, A.S. and Plymate, S.R.: Inhibition Factor of Migration Factor by HCG and Progesterone. Presented to OB/GYN Armed Forces Seminar, Las Vegas, NV, Oct 83.

### DEPARTMENT OF PATHOLOGY

Oberhofer, T.R.: Use of the RapID NH System to Identify *Haemophilus* and *Pasteurella* Species. Presented to American Society of Microbiologists Annual Meeting, 1984.

### DEPARTMENT OF PEDIATRICS

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TITLE: Mechanism of HCG in Spermatogenesis During Testosterone Suppression

PRINCIPAL INVESTIGATOR: COL Stephen R. Plymate, MC

PROFESSIONAL ASSISTANTS: COL Bruce Fariss, MC  
LTC George Ward, VC  
Mina Garrison, MT

WORK UNIT NO: 80/70

#### TECHNICAL OBJECTIVE

To determine if, during testosterone suppression, spermatogenesis which is reinitiated by HCG is due only to a rise in testicular testosterone or if HCG also stimulates androgen binding protein production.

#### METHOD

Three groups of male rats >90 days old (20 rats/group) will be studied. Initially, each animal will have serum drawn for LH, prolactin, FSH, and testosterone, and a unilateral orchiectomy will be done on each animal with the testicular contents assayed for androgen binding protein, testosterone, estradiol, and dihydrotestosterone plus histology. For six weeks, Group I (control group) will be injected with sesame oil alone. Groups 2 and 3 will be injected with testosterone propionate and sesame oil at a dose of 150 µgm/100 gm body weight. Then, for six more weeks both groups will continue to receive the testosterone propionate and Group 3 will also receive the HCG at a dose of 6 U/100 gm body weight daily. Group I will continue to receive the sesame oil alone. At the end of this six week period, each animal will again have serum drawn for prolactin, FSH, LH, and testosterone, and the animal will then be sacrificed with the other testicle removed and assayed for androgen binding protein, testosterone, estradiol, and dihydrotestosterone as well as histology.

#### PROGRESS

The animal work has been completed. During the past year, epididymal androgen binding protein was measured by RIA. It was found that in addition to the decrease in testosterone, there was an increase in the epididymal androgen binding protein in these animals. A final publication is now being prepared.

PRESENTATIONS: Mechanisms of Prolactin Regulation of Testicular Function; Endocrine Society Meeting, 17 Jun 81.  
Abstract #56, p 96.

Effect of Chronic Administration of Testosterone and Human Chorionic Gonadotropin on Testicular Function. Pacific Coast Fertility Society, Palm Springs, CA, 16 Oct 81; abstract #48.

STATUS: (0)

TITLE: The Normal Variation of Blood Volume in Vivarium Dogs

PRINCIPAL INVESTIGATOR: SP5 Andre Mormile

PROFESSIONAL ASSISTANTS: MAJ Stanley P. Liebenberg, VC  
CPT Karl E. Friedl, MSC

WORK UNIT NO: 84/67

#### TECHNICAL OBJECTIVES

To determine the degree of variation in blood volume of vivarium dogs of different breeds and the development of a plasma and blood volume nomogram for use in experimental studies involving dogs.

#### METHOD

Mixed breed mongrels acquired from a single USDA supplier will be evaluated for blood and plasma volumes by the standard Evans Blue method during evaluation of new acquisitions and on the existing stock following several weeks recovery from any experiments. The sampling will include a minimum of 40 mongrels and at least 15 dogs of one sex. The dogs will be anesthetized with I.V. sodium pentobarbital and a cuffed endotracheal tube will be placed to maintain a patent airway. Various parameters including sex, breed derivation, health, fatness, body size and serum chemistries will be noted. After the measurements are taken, both cephalic veins will be catheterized and the dog will be placed in a lateral recumbency position and left quietly for 10 minutes. A reference sample for the spectrophotometer blank will be drawn and hematocrit and hemoglobin will be determined. Four blood samples will be collected at five minute intervals after a precisely timed bolus injection of Evans Blue dye. These will be centrifuged with the reference sample and the plasma will be measured for absorbance. Dye concentrations will be determined by comparison to a standard curve (the plasma reference sample will be used to re-zero the spectrophotometer in order to adequately equate the plasma values to the water blank and standards). Blood and plasma volumes will be calculated from the extrapolated time zero. The ratio of blood volume to the calculated blood volume will be determined. This variance will determine if blood and plasma volumes in these dogs can be accurately equated simply through hematocrit. The other parameters, most importantly ratio of body weight to nose-to-tail base lengths will be studied for their value as predictors for plasma and blood volumes. These parameters will be compared to the standard body weight parameter.

#### PROGRESS

Blood volume decreases in relation to body size. This is probably reflective of adiposity as indicated by a higher correlation between blood volume and body weight after accounting for variations in fasting plasma triglyceride levels or body weight/length (nose-to-tail base)<sup>2</sup>. A reduction in blood volume in relation to body weight was seen in newly acquired USDA supplier dogs after several months in the laboratory kennels. This is taken as further evidence that adiposity (resulting from a more sedentary existence) is related to a lower overall vascular density. Fatness of the dog can be interpreted as a significant variable in the estimation of blood volume from body weight.

STATUS: (C)



## The Effect of *Streptococcus pneumoniae* Infection on the Binding of Thyroxine (T<sub>4</sub>) to Purified Rat Liver Plasma Membranes - Little

membranes will again be pelleted as described above, the supernatants aspirated, and the membranes counted. Non-specific binding will be determined by parallel incubation with excess cold hormone ( $10^{-5}$  M). Scatchard analysis will be used to assess the affinity and maximum binding capacity of the receptor for T<sub>4</sub>. Counting efficiency will be determined by the channel ratio method.

### PROGRESS

(8/82 - 7/84) Hepatic plasma membranes were isolated from control and *Streptococcus pneumoniae* infected rats in order to determine the effect of *S. pneumoniae* infection on the binding capacity and affinity of hepatic plasma membranes for thyroxine (T<sub>4</sub>). Infection did not affect the purity or the yield of isolated membranes. A significant decrease in both total and free serum (T<sub>4</sub>) was observed during infection. Scatchard analysis of membrane binding, determined under optimal conditions, confirmed the presence of high affinity, low capacity sites, as well as low affinity sites for T<sub>4</sub> on membranes isolated from both control and infected rats. T<sub>4</sub> maximum binding capacity (MBC) of the high affinity sites decreased significantly as the infection became more severe. However, the affinity of these receptors did not change. Neither MBC nor affinity of the low affinity sites was altered by infection. The observed decrease in MBC of the high affinity binding sites for T<sub>4</sub> on hepatic plasma membranes cannot account for the decrease in serum T<sub>4</sub> or the hepatic metabolic alterations also known to occur during *S. pneumoniae* infection.

PUBLICATION: Little, J.S. The Effect of *Streptococcus pneumoniae* Infection on the Binding of Thyroxine to Purified Rat Liver Plasma Membranes. *Endocrinology* 114: 411-417, 1984.

PRESENTATIONS: Little, J.S.: Effect of *Streptococcus pneumoniae* Infection on the Binding of Thyroxine to Plasma Membranes Isolated from Rat Liver. Presented: The Society of Armed Forces, Medical Laboratory Scientists, San Antonio, Texas, 19-23 March 1983. *Fed Proc* 12: 27, 1983.

IBID: The Federation of the American Society for Experimental Biology, Chicago, Ill., 10-15 April 1983, *Fed Proc* 42:324, 1983.

STATUS: (C)

TITLE: The Effect of *Streptococcus pneumoniae* Infection on the Binding of Thyroxine (T<sub>4</sub>) to Purified Rat Liver Plasma Membranes

PRINCIPAL INVESTIGATOR: MAJ James S. Little, MSC

PROFESSIONAL ASSISTANT: MAJ Stanley P. Liebenberg, VC

WORK UNIT NO: 82/65

#### TECHNICAL OBJECTIVES

To determine if there are specific receptors for T<sub>4</sub> on hepatic plasma membranes; if these receptors are affected by *S. pneumoniae* infection; and if receptor changes can be correlated with alterations known to occur in hepatic metabolism during infection.

#### METHOD

Male Sprague-Dawley rats (200-250 g) will be maintained on stock Purina lab chow and tap water *ad libitum*. All rats will be acclimated to a 12-hour day-night cycle for 14 days before experimentation to standardize circadian variations. Rats will be inoculated with varying doses ( $3 \times 10^4$  -  $3 \times 10^5$ ;  $6 \times 10^5$  -  $1 \times 10^6$ ; and  $6 \times 10^6$ ) of heat-killed (control) or virulent (infected) colony-forming units of *S. pneumoniae*, serotype I, A-5 strain. After inoculation, all rats will be fasted but allowed access to water and euthanized 40 hours after inoculation, a time corresponding to the midpoint of the night cycle. Fasting of controls will be necessary because infected rats are anorectic. Hepatic plasma membranes will be isolated and the purity assessed. For initial studies to determine optimum time, temperature, protein concentration, and pH, plasma membranes from control or infected animals will be pooled. Once the binding assay has been optimized with respect to time, temperature, plasma membrane protein concentration, and pH, plasma membranes will be prepared from individual control and infected animals. Each control or infected group will contain at least 6 animals. Three groups of infected animals will be studied with each group receiving an increasingly larger dose of *S. pneumoniae*. Receptor assays will be performed in a total volume of 0.2 ml contained in 10x75 mm borosilicate glass test tubes. The assay will contain <sup>125</sup>I T<sub>4</sub> (50,000 to 100,000 counts per minute), from 0 to  $10^{-5}$  M cold T<sub>4</sub>, and plasma membranes at the determined concentration. All components will be diluted in buffer (T<sub>4</sub> Buffer) containing 0.25 M sucrose, 20 mM Tris-Cl, 1 mM MgCl<sub>2</sub>, 2 mM EDTA, 50 mM NaCl, 1 mM dithiothreitol, and 5% (v/v) glycerol. Assays will be performed in triplicate at the optimal temperature and time. Assays will be stopped by the addition of 1.0 ml of ice cold T<sub>4</sub> buffer and centrifugation at 2200 g for 15 minutes. Following centrifugation, the supernatant will be aspirated and the plasma membrane pellets washed by the addition of 1.0 ml of ice cold T<sub>4</sub> buffer. The

Effect of *Streptococcus pneumoniae* Infection on the Binding of  
Insulin to Plasma Membranes Isolated from Rat Liver - Little

slight but not significant increase in the maximum binding capacity (MBC) and no change in the affinity of the receptor for the hormone when the data were expressed per milligram of plasma membrane protein. This observed increase in MBC was larger when the data were expressed on the basis of total liver insulin plasma membrane receptors. Assays performed under optimal conditions at 37°C were similar to those performed at 4°C except there was a significant increase in the MBC when expressed on the basis of milligrams of protein or per total liver. A significant increase in serum insulin was also observed during infection. These results suggest that hepatic insulin receptors are increased during infection and may be involved in mediating some of the observed metabolic alterations which occur during infection.

STATUS: (C)

TITLE: Effect of *Streptococcus pneumoniae* Infection on the Binding of Insulin to Plasma Membranes Isolated from Rat Liver

PRINCIPAL INVESTIGATOR: MAJ James S. Little, MSC

PROFESSIONAL ASSISTANTS: LTC James Anderson, MC  
CPT Jerald Merrill, MSC

WORK UNIT NO: 82/24

#### TECHNICAL OBJECTIVE

To determine if *Streptococcus pneumoniae* infection affects the binding of insulin to hepatic plasma membranes and to determine if observed results can be correlated with hepatic alterations known to occur during this infection.

#### METHOD

Male albino rats (150-250 gm) of the Sprague-Dawley strain will be maintained on stock lab chow and tap water, *ad libitum* and acclimatized to a 12-hr day/night cycle for at least 12 days prior to experimentation in order to eliminate circadian variations. Rats will be inoculated subcutaneously with  $3 \times 10^5$  to  $6 \times 10^5$  heat-killed or virulent *S. pneumoniae* serotype I, A5 strain organisms. At 40 hr post inoculation, plasma membranes will be prepared from both groups of rats. These membranes, which have been shown to be essentially devoid of other cellular contaminants, will be washed by suspension and recentrifugation to remove absorbed cytoplasmic proteins. Preliminary experiments conducted at BAMC will be designed to determine optimum plasma membrane protein concentration, time, pH, and temperature for the binding of labeled insulin to isolated plasma membranes. In a total incubation volume of 450 microliters, buffer, plasma membranes, cold standards, and labeled hormone will be incubated at the predetermined temperature, pH, and time. Non-specific binding is determined by parallel incubation with excess cold hormone. Scatchard analysis will be used to assess affinity and binding capacity of  $^{125}$ I insulin to plasma membranes isolated from 10 control and 10 infected animals. Group mean values will be compared by the unpaired Student's t test and differences will be considered significant at  $P < 0.05$ .

#### PROGRESS

(1/82 - 7/84) Hepatic plasma membranes were isolated from control and *Streptococcus pneumoniae*-infected rats in order to determine the effect of *S. pneumoniae* infection on the binding capacity and affinity of hepatic plasma membranes for insulin. In order to minimize insulin degradation by the membranes during the binding assay, assays were performed at 4°C. It was also shown that degradation could be minimized at 37°C with 1 mM N-ethyl malayamide. Binding assays performed at 4°C under optimal conditions showed a

TITLE: Defining Blood Gas Parameters Using the Saunders Jet Ventilating Device in the Dog in Conjunction with Endoscopic Laryngeal Surgery

PRINCIPAL INVESTIGATOR: MAJ Stanley P. Liebenberg, VC

PROFESSIONAL ASSISTANTS: COL Leonard L. Hays, MC  
MAJ Willis H. Jacob, MSC  
MAJ Del Ray Maughan, MC  
CPT Wallace E. Taylor, MC

WORK UNIT: 82/56

#### TECHNICAL OBJECTIVE

To define blood gas and blood pH levels in the dog using the Saunders jet ventilating device.

#### METHOD

Six dogs will be studied. After each dog has been anesthetized with ultrashort-acting barbiturate and before actual tissue excision with the CO<sub>2</sub> laser commences, a femoral arterial cutdown will be performed. Arterial catheterization will be made under direct visualization by insertion of an Intracath. After ligatures are securely placed around the Intracath to prevent accidental withdrawal, a 3-way stopcock will be placed on the end of the catheter, the catheter will be flushed with 10% heparinized saline to prevent clot formation, and then the catheter will be connected to a Hewlett-Packard Model 7700 8-channel physiograph machine for BP and EKG monitoring. Ventilation with the Saunders device will be performed at varying rates (4, 5, 7.5, 12, and 30 times/minute) for 5 minutes each. The duration of each burst of oxygen will be approximately one second. An initial arterial blood sample will be drawn for O<sub>2</sub>, CO<sub>2</sub>, and pH determinations prior to any ventilation with the Saunders device. Further blood samples for the same parameters will be drawn at the end of each 5 minute ventilation period. The study will commence with the most rapid rate and proceed in order to the slowest rate. After completion of all ventilation periods, the Intracath will be withdrawn.

#### PROGRESS

(5/82 - 8/84) Due to the transfer of the original principal investigator, no work was conducted on this project before MAJ Liebenberg agreed to become the principal investigator. Due to scheduling conflicts, time could never be mutually established between MAJ Liebenberg before his reassignment and the investigators from the otolaryngology service which maintained the needed equipment and employed the technician to operate the equipment; therefore it was terminated.

STATUS: (T)

TITLE: The Effect of 2- $\alpha$ -Hydroxy-4-Pregnen-3-One Treatment on Spermatogenesis and Gonadotrophins in Rats - Friedl

Testes will be sectioned at 4 microns and the slides will be stained with PAS and hematoxylin. The slides will then be studied in the following quantitative manner. Twenty round tubules representing 7th stage cellular associations will be used per animal. Inner and outer tubule diameters will be measured. Spermatogonia, spermatocytes, and S7 spermatids will be counted and expressed in terms of Sertoli cell nuclei counts. Unusual features such as necrotic germ cells and high lipid content of the Sertoli cells will be noted. Leydig cell tissue volumes may be morphometrically measured if preliminary findings are indicative of differences. Means of all counts and tubule diameters will be compared between the four groups by t test.

Steroids and gonadotrophins will be measured for all eight groups by radioimmunoassay and these values will also be compared between intact groups and castrated groups by t test. The relationship between the quantitative assessment of spermatogenesis and hormonal changes will be compared between intact groups.

#### PROGRESS

Sixty-four (64) rats have been studied. Hormonal data indicate that 20 $\alpha$ -OHP acts on both the hypothalamic/pituitary and the testis mechanisms. The actions result in a substantial activation of the seminiferous tubule component of the testes as demonstrated by significant increases in androgen binding protein concentrations. A quantitative assessment of spermatogenesis is currently underway from the completed histological preparations. Completion of this study will require approximately 95 hours of microscope work.

STATUS: (O)

TITLE: The Effect of 2- $\alpha$ -Hydroxy-4-Pregnen-3-One Treatment on  
Spermatogenesis and Gonadotrophins in Rats

PRINCIPAL INVESTIGATOR: CPT Karl E. Friedl, MSC

PROFESSIONAL ASSISTANTS: COL Bruce L. Fariss, MC  
COL Stephen R. Plymate, MC  
LTC James L. Kelley, MC  
Mina Garrison, DAC, B.S., M.T.

WORK UNIT NO: 83/64

#### TECHNICAL OBJECTIVE

To examine the possibility of a physiological role for the steroid metabolite 2- $\alpha$ -hydroxy-4-pregnen-3-one in the hypothalamic-pituitary-testes axis. The effect on gonadotrophins will be studied in castrated animals and the effect on spermatogenesis through both direct actions on the testes and indirect actions through any effects on gonadotrophins will be observed.

#### METHOD

Thirty-two young adult male rats (250 gms) will be anesthetized with ketamine and castrated on the day prior to the start of treatments. These animals will be randomly distributed into four treatment groups. In a second experiment, thirty-two intact rats from the same shipment will also be randomized into four treatment groups. In both experiments, the groups will be injected daily for 30 days with 1 mg progesterone, 1 mg 2- $\alpha$ -OHP, 5 mg 2- $\alpha$ -OHP, or sesame oil. The steroids will be dissolved in sesame oil and animals will receive 0.2 ml volumes I.M.

After 30 days of treatment the rats will be guillotined and trunk blood will be collected into heparinized containers, centrifuged and plasma aliquots for the hormone assay will be made and stored at -80°C.

The testes will be removed from the intact animals, decapsulated and weighed. The left testis will be divided and preserved for histology. The right testis will be frozen at -80°C until assay of intratesticular T, E<sub>2</sub>, and androgen binding protein (ABP). For all animals, the ventral prostate and seminal vesicles will be ligated, removed and weighed. Epididymides will also be weighed (from intact animals) and the right epididymis will be frozen at -80°C for later assay of T, E<sub>2</sub>, and ABP. Adrenals will be collected and weighed from all animals and preserved for possible later histological study.

TITLE: Evaluation of the Hypothalamic-Pituitary-Adrenal (HPA) Axis in Psychiatric Patients Who Do Not Suppress Serum Cortisol After Overnight Dexamethasone.

PRINCIPAL INVESTIGATOR: COL Bruce L. Fariss, MC

PROFESSIONAL ASSISTANTS: LTC Stephen R. Plymate, MC  
Thomas H. Lampe, M.D.  
Steven C. Risse, M.D.

WORK UNIT NO: 83/86

#### TECHNICAL OBJECTIVE

To determine whether psychiatric patients who do not suppress serum cortisol after the overnight dexamethasone suppression test will suppress cortisol production after the more extensive dexamethasone suppression test developed for the diagnosis of Cushing's disease.

#### METHOD

Patient Selection: Fifteen psychiatric in-patients at American Lake VA Medical Center who have been found to be nonsuppressors from a dexamethasone suppression test.

Patient Exclusion: A diagnosis or past history of pituitary or adrenal disease or if they, in the opinion of the investigators, have medical conditions or receive medications that have been reported to give a "false" nonsuppression to dexamethasone.

Procedures: Baseline 0800 cortisols will be obtained on all subjects prior to beginning the study.

Days 1 and 2: 0.5 mg of dexamethasone by mouth every six hours with blood samples for serum cortisol collected at 1600 on Day 2.

Days 3 and 4: 2 mg of dexamethasone by mouth every 6 hours with blood samples for serum cortisol drawn at 1600 on Day 4.

Whenever possible 24 hour urines for creatinine, total volume and hydroxycorticosteroids will be obtained the day before and each day of the dexamethasone testing. Within one week of completion of the above testing, an overnight dexamethasone suppression test will be readministered to ascertain the constancy of response to this test. A diagnostic interview for purposes of diagnosis by DSM-III criteria and a BPRS will be performed on each subject.

#### PROGRESS

(9/83 - 8/84) Twelve patients were studied. Two days of dexamethasone caused the plasma cortisol to suppress in the non-suppressible dexamethasone psychiatric, except in patients who were taking estrogen or other medications related to abnormal dexamethasone metabolism such as dilantin. Twenty-four hour urinary free cortisols were within the range of normal in all patients measured.

STATUS: (C)



TITLE: Adrenal Hyperplasia in Pacific Salmon

PRINCIPAL INVESTIGATOR: COL Bruce L. Fariss, MC

PROFESSIONAL ASSISTANT: COL Stephen Plymate, MC

WORK UNIT NO: 80/01

#### TECHNICAL OBJECTIVE

To determine if the administration of a salt-retaining hormone, desoxycorticosterone, will prevent adrenal gland hyperplasia in the Pacific salmon and to determine if the Pacific salmon can spawn and survive.

#### METHOD

It is proposed that a total of 20 Pacific salmon be captured while in salt water. These fish are to be sexually mature and will be retained in holding pens. Half of the fish will be treated with desoxycorticosterone in oil, intramuscularly. Blood samples will be obtained from the fish for the measurement of plasma hydroxycorticosteroid, desoxycorticosterone, and aldosterone. Following the administration of the desoxycorticosterone, all of the fish (treated and controls) will be placed in a holding tank until spawning occurs. Following spawning, the fish will be returned to the holding pen in the salt water for follow-up observations of survival.

#### PROGRESS

(11/79 - 8/84) A total of 392 fish was studied. Cortisol response to ACTH was exaggerated at times in the mature fish; however, when this was carefully studied it appeared to be seasonal rather than related to sexual maturity. Intravenous insulin-induced hypoglycemia causes similar responses in plasma cortisol, but it was necessary to look at the fish 5-8 hours after the injections.

PRESENTATION: Fariss, B.L., Mallouf, J., Ward, G.S., Liebenberg, S.P., and Plymate, S.R.: Evaluation of Pituitary-Adrenal Axis in the Pacific Coast Silver Salmon (*Oncorhynchus kisutch*). Society of Military Endocrinologists, 15 Jun 82, San Francisco, CA.

STATUS: (C)

TITLE: The Effects of Chronic Hyperglycemia on Pregnancies and Fetuses in Sheep During Gestation

PRINCIPAL INVESTIGATOR: COL Bruce L. Fariss, MC

PROFESSIONAL ASSISTANTS: LTC Paul B. Jennings, VC  
LTC George S. Ward, VC

WORK UNIT NO: 74/06

#### TECHNICAL OBJECTIVE

The objectives of this project are to determine the effects of hyperglycemia upon pregnancies as manifested by frequency of abortions and hydramnios and possible developmental abnormalities of the fetuses.

#### METHOD

The study will be composed of three groups of pregnant ewes with as close proximity of the date of conception as possible. All groups will be given food and water *ad libitum*. Group I: This will be the control group of six animals with no treatment. Group II: Seven animals which have undergone subtotal pancreatectomy. The diabetes mellitus produced surgically will be managed by the injection of intermediate acting insulin such as NPH. Blood sugars will be monitored frequently as indicated clinically. Group III: Seven animals which have indwelling catheters for infusion of hypertonic sugar solutions with a lambda infusion system. The systems are portable, weighing less than 3 pounds and can be strapped to the backs of the animals without difficulty. Blood sugars will be monitored at frequent intervals with an attempt to keep blood sugars between 200 and 300 mg/100 ml of blood at all times.

The course of the pregnancies will be observed for each group of animals. Blood sugars for each group will be determined at frequent intervals during the gestation. At delivery the neonate will be examined pathologically for evidence of pulmonary, liver, pancreatic, kidney, and possible developmental abnormalities.

#### PROGRESS

(10/73 - 8/84) Total pancreatectomy does not cause blood sugars to rise in sheep. Sodium butyrate in normal sheep is associated with a rise in blood sugar, insulin, and glucagon. Following pancreatectomy, blood sugar rises slightly; however, insulin and glucagon do not rise.

PRESENTATION: Fariss, B.L., Hane, S., Rodd, G., Jacob, W.H., and Plymate, S.R.: Pancreatectomized Sheep Do Not Develop Overt Diabetes Mellitus. Presented to Society of Uniformed Endocrinologists Annual Meeting, San Antonio, Texas, 7-8 June 1983.

STATUS: (C)

DETAIL SHEETS  
FOR  
PROTOCOLS

DEPARTMENT OF CLINICAL INVESTIGATION

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TITLE: Testosterone and HCG Effects on Testicular Steroidogenesis

PRINCIPAL INVESTIGATOR: COL Stephen R. Plymate, MC

PROFESSIONAL ASSISTANTS: COL Bruce L. Fariss, MC  
MAJ Stanley Liebenberg, VC  
MAJ Allan Avbel, MC  
SSG James Hayes  
Louis Matej, B.S.

WORK UNIT NO: 81/92

#### TECHNICAL OBJECTIVE

To determine the mechanism of inhibition of intratesticular testosterone production by HCG and testosterone.

#### METHOD

Six groups of adult male Wistar rats >250 gm will have baseline serum drawn for LH, FSH, and testosterone. All animals will be kept on a 14 hour light, 10 hour dark cycle. Group A will receive sesame oil twice weekly for 12 weeks. Group B will receive 150 µgm/100 gm BW testosterone enanthate twice weekly for 12 weeks. Group C will receive 150 µgm/100 gm BW testosterone enanthate twice weekly for six weeks and the same regimen plus 18 U HCG QD for an additional six weeks. Group D will receive 300 µgm/100 gm BW testosterone enanthate for six weeks and the same regimen plus 18 U HCG QD for an additional six weeks. Group E will receive 150 µgm testosterone enanthate/100 gm BW plus 18 U HCG twice weekly for six weeks, and the same regimen plus the addition of Teslac 5 µgm daily for six more weeks. Group F will receive 150 µgm testosterone enanthate/100 gm BW twice weekly for six weeks and then 18 U HCG daily plus 10 mg Teslac twice a day for six weeks. After the 12 weeks, blood will again be drawn, the animals sacrificed, the testes, and epididymis removed, weighed, and frozen. Intratesticular DHT, E<sub>2</sub>, and ABP will be measured in the testicle and androgen binding protein measured in the epididymis. Histology will be performed to include mean seminiferous tubule diameters.

#### PROGRESS

(7/81 - 9/84) This study demonstrated that administration of testosterone and HCG had a greater effect on suppression of testicular testosterone levels than administration of testosterone alone. Testosterone alone lowered intratesticular testosterone by LH suppression and increased intratesticular E<sub>2</sub>. The combined effect of HCG and testosterone appeared to be by further increases in intratesticular E<sub>2</sub> as well as greater suppression of serum LH. A paper is being finalized for submission for publication.

PRESENTATION: Influence of Long Term Testosterone (T) and Human Chorionic Gonadotropin (HCG) Administration on Intratesticular Testosterone. 3rd Annual Military Endocrinologists Meeting, San Francisco, CA, 15 June 1982.

STATUS: (C)

TITLE: Differentiation of Luteinizing Hormones From Different  
Animal Species Utilizing the HPLC

PRINCIPAL INVESTIGATOR: COL Stephen R. Plymate, MC

PROFESSIONAL ASSISTANTS: COL Bruce L. Fariss, MC  
MAJ Willis H. Jacob, MSC

WORK UNIT NO: 82/23

#### TECHNICAL OBJECTIVE

To determine if high pressure liquid chromatography can be a means by which the pituitary gonadotrophins can be separated and quantitated between species.

#### METHOD

Various nanogram amounts of LH ranging from 1-50 ng/ml will be assayed by the HPLC using the protein 125 column. Human, primate, ovine, rat, and rabbit LH will be assayed. Human LH which has been labelled by chloramine-T or lactoperoxidase will also be used. The same concentrations of LH will then be added to the mouse Leydig's cell bioassay system. The results between these two techniques will be compared as well as the points at which the various LH's are detected on the HPLC. The statistical analysis will be performed by linear regression and T tests.

#### PROGRESS

Blood samples were drawn on 17 patients at the Burn Unit at Ft Sam Houston. It was noted that they have measureable radio-immunoassayable LH but unmeasureable bioassayable LH activity. These samples have begun to be processed through the HPLC to determine differences in molecular weight and cyolic acid moieties.

STATUS: (O)

TITLE: Effect of HCG and T on Regulation of Leydig Cell Function

PRINCIPAL INVESTIGATOR: COL Stephen R. Plymate, MC

PROFESSIONAL ASSISTANTS: COL Bruce L. Fariss, MC  
MAJ James S. Little, MSC  
John White, Ph.D.  
Mina Garrison, M.T.  
Louis Matej, M.T.

WORK UNIT NO: 82/67

#### TECHNICAL OBJECTIVE

To expand further the studies which the investigators have reported showing the relationship between LH and testosterone (T) in regulating T production. This study is designed to determine the time course of events following HCG administration to T-suppressed animals by determining changes in intratesticular T and LH receptors at specified intervals following HCG administration.

#### METHOD

Male Wister rats >90 days and weighing 200-250 gms will be given T-enanthate 150 µgm/100 gm body weight IM biweekly for six weeks and control animals will be injected with sesame oil (time zero). Eight control and eight treatment animals will be sacrificed at this point. Then HCG, 18 IU each day, will be started on all animals treated with T and control animals will be injected daily with saline. Eight control and eight treatment animals will be sacrificed at 3, 7, 14, 28, and 56 days after time zero and trunk blood collected. Testes and epididymae will be removed, trimmed of fat, weighed, and frozen at -70°C until assayed. Serum will be analyzed for T and LH. Testes will be analyzed for T, E<sub>2</sub>, ABP, and HCG receptors. Testes from six control and six treatment animals sacrificed at 7, 28, and 56 days will be prepared for electronmicroscopy. Electronmicroscopy and stereological analysis of the smooth endoplasmic reticulum in the Leydig cells will be performed. Serum T and LH will be performed by RIA. The testes will be cut in half. One half along with the epididymis, will be homogenized in a phosphosaline buffer pH 7.4 with 6 ml used per gm of tissue. This homogenate will then be assayed for T, E<sub>2</sub>, and ABP and results expressed per ng of protein. The other half of the testes will then be assayed for HCG/LH receptors. Comparison between groups will be made using the non-paired Student's T test or non-parametric tests.

#### PROGRESS

(8/82 - 9/84) HCG suppression of testosterone production in the testicles of T-treated rats is such that within the first week of HCG administration there is an increase in intratesticular T. It is only after there has been a decrease in HCG receptors during the third, fourth, and fifth weeks of treatment that intratesticular T begins to decrease.

STATUS: (C)

TITLE: Evaluation of Metabolic Effects of Micronized Oral  
Estradiol and Progesterone Combinations

PRINCIPAL INVESTIGATOR: COL Stephen R. Plymate, MC

PROFESSIONAL ASSISTANTS: Donald E. Moore, M.D., Univ of Washington  
Robert H. Knopp, M.D., Univ of Washington  
Louis Matej, M.T., DAC

WORK UNIT NO: 83/11

#### TECHNICAL OBJECTIVE

To test basic biochemical parameters of toxicity in women ingesting combinations of estradiol/norgestrel as an oral contraceptive. Acceptability, relative potency, and ovulation suppressive ability will be tested.

#### METHOD

Two studies are planned. In the first study, after one control non-treatment cycle, 4 groups of 12 women will daily ingest various combinations of norgestrel plus estradiol, for 21 days out of a 28 day cycle. D-1-norgestrel (300 µg) or levonorgestrel (150 µg) and 0.5, 1, 2, and 4 mg of micronized estradiol will be tested. A control group of 12 women will ingest 300 µg of d,l-norgestrel or 150 µg of levonorgestrel plus 30 µg of ethinyl estradiol. Serum levels of progesterone will be obtained weekly in order to detect any ovulation. Any abnormal bleeding, nausea, headaches, or other symptoms will be recorded. Pharmacodynamic responses will be studied by measuring serum levels of estrone and estradiol. Relative estrogen potencies will be compared by measuring serum levels of sex steroid binding protein (SBP-BC). Biochemical measures of liver and renal function, the coagulation, lipid, cholesterol, and endocrine systems will also be studied. Each subject's non-treatment cycle biochemical levels will act as a control value. Data will be analyzed using the paired t test or the Wilcoxon matched-pairs signed-ranks test.

In the second study, the one combination from the first study that is associated with no evidence of ovulation, good menstrual cycle control, tolerable side effects, little or no change in the biochemical parameters, and little or no elevation of SBP-BC will be given to 60 women for 6 cycles, preceded by one control non-treatment cycle and followed by two control non-treatment cycles. The same control medication as above will be used in a group of 24 women. The same biochemical tests will be performed. If toxicity indices are low, the medication is well tolerated, and ovulation is completely inhibited, further clinical trials using lower combinations of norgestrel and estradiol will be proposed.

#### PROGRESS

(10/82 - 9/84) Using micronized oral estradiol vs oral ethinyl estradiol as the estrogen in a combination oral contraceptive, the investigators felt that the micronized estradiol was not well absorbed, did not prevent break-through bleeding, and did not overcome the effect of progesterone in lowering HDL cholesterol or TEBG.

STATUS: (C)



**TITLE:** Relationship of Body Fat to Control of Synthesis by the Liver of Testosterone Estradiol Binding Globulin (TeBG) and Sex Hormones

**PRINCIPAL INVESTIGATOR:** COL Stephen R. Plymate, MC

**PROFESSIONAL ASSISTANTS:** COL Bruce L. Fariss, MC  
LTC Gary L. Treece, MC  
MAJ Stanley P. Liebenberg, VC  
CPT Karl E. Friedl, MSC  
Mina J. Garrison, DAC, M.T.  
Louis A. Matej, DAC, M.T.

**WORK UNIT NO:** 83/83

#### TECHNICAL OBJECTIVE

To determine the metabolic parameters responsible for modifying production of TeBG in weight gain.

#### METHOD

Six female beagles, not in estrus, will have 3 baseline serums drawn for T<sub>4</sub>, T<sub>3</sub> uptake, T<sub>3</sub> RIA, TeBG, testosterone, androstenedione, and estradiol weekly for a 3-week baseline period. The animals will be weighed weekly and then allowed unlimited access to food with decreased exercise. Weekly blood samples will again be drawn until the animals have gained 30% of their starting body weight. At that point, the animal's food intake will be determined and the weight maintained at the 30% level. The animals will then be given two subcutaneous injections (two days apart) of estradiol valerate (40 mg). One and two weeks after the last injection, blood samples will again be drawn. Next, the animals will be given tamoxifen, an antiestrogen, at a dose of 10 mg t.i.d. intramuscularly and TeBG levels again drawn one week and two weeks after tamoxifen administration. The animals will then be allowed one month's rest while maintaining their weight at 30% above their ideal body weight. Baseline studies as mentioned above will then be obtained weekly for two weeks. Then the animals will be given 1 mg of levothyroxine intramuscularly weekly for two weeks, and blood studies will be repeated at the time of the second injection and for three weeks after the administration of levothyroxine. A similar group of six normal weight female beagles, age-matched and not in estrus, will be studied with similar blood drawings and administration of medications.

#### PROGRESS

Twelve female beagles are being used on this project. Baseline blood samples have been drawn. However, because of the moratorium on the use of dogs in clinical research initiated by DoD, this project is currently suspended.

**STATUS:** Suspended

TITLE: Evaluation of Efficacy of Varicocele Repair

PRINCIPAL INVESTIGATOR: COL Stephen R. Plymate, MC

PROFESSIONAL ASSISTANTS: MAJ Brian Miles, MC  
C. A. Paulsen, M.D.  
Richard E. Burger, M.D.

WORK UNIT NO: 83/84

#### TECHNICAL OBJECTIVE

To determine the efficacy of varicocele repair in improving fertility in the infertile male.

#### METHOD

Four groups (75 men each) will be studied: (1) infertile men who are going to have their varicoceles repaired, (2) infertile men without varicoceles; (3) fertile men who have varicoceles, and (4) fertile men without varicoceles. Prior to entering into this study all subjects will have a complete history and physical examination done, including assessment of the presence or absence of a varicocele as well as calibrated measurement of testicular size. Each group will have eight to ten semen analyses performed, two sperm penetration assays performed at least four weeks apart, and two LH/RH stimulation tests performed using 200 mg of LH/RH. Blood samples will be drawn every 15 minutes for two hours after the injection of the LH/RH. Following repair of the varicocele, the men will have a seminal fluid analysis performed every two to four weeks, sperm penetration assay performed at six months and twelve months after the varicocele ligation, and LH/RH again performed at six and twelve months after the varicocele ligation.

#### PROGRESS

Approximately 90 subjects have been studied. Thus far it has been found that fertile men with varicoceles have sperm counts and LH and RH tests that are intermediate between infertile men with varicocele and normal non-varicocele fertile men. In addition, there is a great overlap in the sperm penetration assay between normal fertile men and infertile men. This problem appears to be resolved by introducing time capacitation in the sperm by administering a calcium ionophore.

STATUS: (O)

TITLE: Role of Depression in Modulation of Hypothalamic-Pituitary-Gonadal-Axis

PRINCIPAL INVESTIGATOR: COL Stephen R. Plymate, MC

PROFESSIONAL ASSISTANTS: COL Bruce L. Fariss, MC  
Thomas Lampe, MD, American Lake VA Hospital  
Steve R. Risse, MD, American Lake VA Hospital

WORK UNIT NO: 83/85

#### TECHNICAL OBJECTIVE

To evaluate the hypothalamic gonadal function in a biochemically defined depressive state in order to further define the role of neurotransmitters in both the depression and the control of the hypothalamic-pituitary-gonadal (HPG) axis.

#### METHOD

Subjects: Ten women and ten men admitted for depression who have nonsuppressible DST as defined by a cortisol level greater than 5  $\mu\text{g/dl}$  after 1 mg dexamethasone given at 2300 hours and plasma cortisol measured at 0800, 1600, and 2300 hours the following day. Following the DST at 0800 hours, a 200 mg bolus of LH/RH will be given IV. Blood samples will be drawn at -15, 0, 15, 30, 45 and 60 minutes for LH, FSH, and prolactin. This will be followed by a 100  $\mu\text{g}$  bolus of TRH with blood samples drawn at 60, 75, 90, 105 and 120 minutes for prolactin, TSH and growth hormone. When the DST returns to normal the studies will be repeated on all patients. Any patients on phenothiazines will be excluded from the study. In addition the -15 and zero time samples will have  $\beta$ -lipotropin, ACTH,  $\beta$ -endorphin, testosterone, estradiol, and sex hormone binding globulin measured. The female patients will have a menstrual history noted. If they are cycling, the time of the blood drawing in relationship to their cycle will be calculated and confirmed by measurement of serum progesterone.

#### PROGRESS

At the present time, the investigators have found that in four Alzheimer's patients given three different stimulatory doses of TRF, there is a paradoxical rise in luteinizing hormone.

STATUS: (0)

TITLE: Levothyroxine Therapy in Oligospermic Men

PRINCIPAL INVESTIGATOR: COL Stephen R. Plymate, MC

PROFESSIONAL ASSISTANTS: MAJ Wayman W. Cheatham, MC  
Louis A Matej, DAC

WORK UNIT NO: 84/31

#### TECHNICAL OBJECTIVE

To assess whether levothyroxine therapy in physiologic doses is associated with significant changes in sperm analysis in a group of idiopathically oligospermic men.

#### METHOD

Twenty males with a diagnosis of idiopathic oligospermia who have been evaluated for infertility be studied. Idiopathic oligospermia as a diagnosis will result when the individual has sperm density of  $<20 \times 10^6$  sperm/cc or  $<60 \times 10^6$  sperm/ejaculate with or without impaired motility; normal buccal smear and/or karyotype; normal testosterone; normal estradiol and prolactin; no evidence of abnormality of the hypothalamic pituitary axis; normal basal triiodothyronine ( $T_3$ RIA), thyroxine ( $T_4$ ),  $T_3$  resin uptake ( $T_3$ U), and TSH; and no history of cryptorchidism or orchitis.

Excluded from the study will be individuals  $<18$  or  $>60$  years old or with evidence or history of valvular or ischemic heart disease or cardiac dysrhythmia; systolic blood pressure  $>140$  mm Hg or diastolic blood pressure  $>90$  mm Hg; creatinine  $>1.4$  mg/dl, BUN  $>20$  mg/dl or liver enzymes outside the established range of normal; evidence of a disorder of primary sexual differentiation; a varicocele; or taking medication known to have an effect on the reproductive axis.

Individuals who qualify under these criteria will be randomly assigned to one of two groups. Baseline testosterone, LH, FSH, estradiol, prolactin,  $T_3$ U,  $T_4$  and  $T_3$  RIA will be drawn and a TRH stimulation test using 500  $\mu$ g TRH will be administered to both groups with blood samples taken at 0 and +30 mins. For documentation purposes a karyotype will be done. Members of both groups will also collect three separate baseline semen specimens at intervals of at least 7 days with 48 hrs abstinence prior to each collection. Data to be collected from the semen analysis will include subject, date, color, turbidity volume, pH, sperm count per cc, morphology immediate motility, and 2 hr motility. Group A will be given L-thyroxine daily, beginning after the baseline studies are completed and continuing for 120 days. Three weeks prior to the termination of the treatment period, the subject will initiate a repetition of the semen collection sequence.

## Levothyroxine Therapy in Oligospermic Men - Plymate

Collection of blood for hormonal studies and a TRH stimulation test as performed prior to the beginning of the treatment period will be repeated at this time.

Members of Group B will be given a placebo. The treatment period, the semen collection, and blood test sequence will be identical to those described for Group A.

At the end of the first 120 day treatment period, members of the two groups will cross over such that those previously taking active hormone will take placebo and those formerly taking placebo will take active hormone. The individuals will then duplicate the first 120 day treatment period. At the end of the second 120 day period, the individuals will cease all medications and be released from the protocol but will continue to receive appropriate follow-up evaluation for their primary disorder.

Subjects will be evaluated in the clinic monthly during the 240 day study period or more often as they desire if questions arise. Any subject who demonstrates clinical symptoms suspicious of hyperthyroidism while under study will immediately cease all medication and have blood drawn for  $T_3U$ ,  $T_4$  and  $T_3(RIA)$  and a physical examination. If hyperthyroidism is confirmed, the subject will be excused from the study.

### PROGRESS

Due to completion of an on-going protocol for treatment of oligospermic men, no patients have been entered in this study to date.

STATUS: (0)

TITLE: Relationship of Endogenous Sex Hormones to Lipids and Arteriosclerotic Coronary Vascular Disease (ASCVD)

PRINCIPAL INVESTIGATOR: COL Stephen R. Plymate, MC

PROFESSIONAL ASSISTANTS: CPT Karl E. Friedl, MSC  
John Barron, M.D., Dartmouth Medical School  
Louis A. Matej, GS/09

WORK UNIT NO: 84/85

#### TECHNICAL OBJECTIVE

To define the relationships between estrogens, androgens, and certain risk factors for ASCVD in men.

#### METHOD

Serum sex hormones and lipoproteins will be measured in three groups; one diseased and two control groups: (1) Patients with severe coronary artery disease demonstrated by coronary arteriography; (2) patients with absent or minimal coronary artery disease demonstrated by coronary arteriography within the past year; and (3) patients with no history or symptoms of coronary arteries unexamined. All subjects will be white males between the ages of 35 and 75 years and will be from among in-patients who are having coronary arteriography. Patients with advanced liver disease, chronic adrenal failure, or steroid hormone therapy will be excluded from all study groups. The admitting diagnosis for subjects will be unrelated to coronary artery disease or alterations in steroid hormones. Fifteen ml of serum will be drawn on each subject at the time of routine pre-arteriography or surgical blood drawing. Serum hormone measurements will include total serum estradiol, total serum testosterone by RIA, serum sex hormone binding globulin by saturation analysis, serum free estradiol and free testosterone by centrifugation dialysis, serum total cholesterol by the cholinesterase method, and serum HDL cholesterol by heparin manganese precipitation. First, we will compare mean hormone levels using standard t tests in related confidence intervals. If certain covariants are found to be associated with the hormone levels, then they can be adjusted for with an analysis of covariants. We will also compute the relative risk odds ratio associated with various serum estrogen ranges. Adjustments for covariants will be accomplished using logistic modelling. This technique will also allow us to assess the importance of other coronary vascular disease risk factors in influencing a relationship under study.

#### PROGRESS

Patients with known coronary artery disease (83) and 83 matched controls without evidence of coronary artery disease have had blood samples drawn which are presently being analyzed for HDL and LDL cholesterol, testosterone, estradiol, free testosterone and estradiol by dialysis and sex hormone binding globulin assay.

STATUS: (0)

DETAIL SHEETS  
FOR  
PROTOCOLS

DEPARTMENT OF EMERGENCY MEDICINE

TITLE: Emergency Room Procedure Training

PRINCIPAL INVESTIGATOR: COL Frederick Burkle, MC

PROFESSIONAL ASSISTANTS: LTC Samuel T. Coleridge, MC  
MAJ Steven C. Dronen, MC  
MAJ Stanley P. Liebenberg, VC

WORK UNIT NO: 82/25

#### TECHNICAL OBJECTIVE

To provide training to acquire the necessary manipulative skills in performing invasive, life-saving procedures for the Emergency Medicine Residency Program.

#### METHOD

The procedures listed below will be performed in two separate sessions under the supervision of a staff member and the veterinarian assigned to Clinical Investigation. All animals will be anesthetized and then will be sacrificed immediately after the procedures.

##### PART I:

1. Femoral vein cutdown
2. Peritoneal lavage
3. Tube thoracostomy
4. Thoracotomy
5. Aortic cross-clamping
6. Control of pulmonary hemorrhage
7. Cardiac wound repair
8. Endotracheal intubation
9. Percutaneous transtracheal ventilation
10. Cricothyroidotomy

##### PART II:

1. Tissue pressure monitoring
2. Arterial pressure monitoring
3. Swan-Ganz catheter placement
4. Transvenous ventricular pacemaker placement
5. Transthoracic ventricular pacemaker placement
6. Pericardiocentesis
7. Segstaken-Blakemore tube placement
8. Auto transfusion from hemothorax
9. Twist drill decompression
10. Skull Trephination

#### PROGRESS

Dr. Burkle became the principal investigator on this protocol upon the departure of Dr. Dronen.

There were no training sessions due to the difficulty of obtaining animals and because of the moratorium on the use of dogs in clinical research initiated by DoD. This project is currently suspended due to the moratorium.

STATUS: Suspended



TITLE: The Role of Plain Abdominal Radiographs in the Evaluation of Acute Gastrointestinal Hemorrhage

PRINCIPAL INVESTIGATOR: CPT Marc A. DiJulio, MC

PROFESSIONAL ASSISTANTS: CPT Leonard M. Checchio, MC

WORK UNIT NO: 84/24

#### TECHNICAL OBJECTIVE

To determine if routine ordering of acute abdominal series (AAS) in gastrointestinal hemorrhage is warranted or if particular clinical symptoms or signs identify patients in whom the AAS will provide information that aids in diagnosis or management.

#### METHOD

Patients admitted during the past 24 to 36 months with the diagnosis of acute gastrointestinal hemorrhage will be entered through a computer generated list based on admitting diagnosis. Emergency Department and in-patient records will be reviewed to gather clinical data such as presenting symptoms and signs and physical examination findings as well as laboratory and radiographic findings. Using this data, a cost effectiveness analysis will be generated to define the clinical value of the plain abdominal radiograph in this setting. An attempt will be made to identify clinical characteristics that define subgroups of patients in whom the AAS is valuable.

Likelihood ratios will be generated for various clinical variables as frequency of the variables in patients with abnormal radiographs divided by the frequency of that variable in patients with a normal radiograph. Likelihood ratios greater than one associate the variable with a higher probability of an abnormal film. Costs of the films in terms of radiation exposure as well as monetary costs will be compared to the number of films that were valuable in the sense of aiding diagnosis and management.

#### PROGRESS

This study has been completed and a paper is being prepared.

STATUS: (C)

TITLE: The Use of Naloxone in the Management of Hemorrhagic Shock

PRINCIPAL INVESTIGATOR: MAJ Steven C. Dronen, MC

PROFESSIONAL ASSISTANTS: CPT Richard Foutch, MC  
CPT Karl Friedl, MSC  
CPT Peter Maningas, MC

ORK UNIT NO: 83/82

#### TECHNICAL OBJECTIVE

o evaluate the effect of the opiate antagonist naloxone on various cardiovascular and biochemical parameters in the setting of hemorrhagic shock.

#### METHOD

Twelve (12) dogs will be divided into three groups. Group I dogs (six) will receive naloxone, a 2 mg/kg bolus followed by 2 mg/kg/hr as an infusion prior to phlebotomy. They will then be bled and reinfused according to the protocol described below. Group II dogs (three) will be bled and reinfused according to the protocol. Group III dogs (three) will not be bled or reinfused but will undergo all other steps in the protocol as described below, receiving naloxone in the same fashion as Group I.

Each dog will be given water but no food 18-24 hours prior to experimentation. The dogs will be anesthetized 30 minutes prior to phlebotomy with 30 mg/kg of IV pentobarbital. Additional anesthesia will be in 2 mg/kg increments to maintain the desired level of sedation. The dogs will be placed in the left lateral recubitus position and tracheally intubated with a cuffed tube.

Swan-Ganz catheter will be placed via cutdown on the right external jugular vein. The left femoral artery will be cannulated with PE 205 tubing. Vascular pressures (blood pressure, central venous pressure, and pulmonary capillary wedge pressure) will be measured by quartz transducers and recorded on a multichannel oscillograph. Blood pressure measurements will be interrupted only for blood sampling and phlebotomy. Central venous pressure measurements will be continuous. After two-point calibration,  $t_{c}O_2$  and  $P_{t_c}CO_2$  electrodes will be placed on the abdomen of the dog. The electrode temperatures will be 44° and 45°, respectively.

Baseline arterial, venous, and mixed venous blood samples will be drawn prior to hemorrhage for determination of control pH,  $pO_2$ ,  $CO_2$ ,  $MVO_2$ , Hgb, and serum lactate. Cardiac output will be determined by the standard thermodilution technique. Simultaneous recording of  $P_{t_c}O_2$  and  $P_{t_c}CO_2$  will be done at each sampling period.

TITLE: Cis-Platinum, 5-FU Chemotherapy of Advanced Head and Neck Squamous Cell Carcinoma (Stage III and Stage IV)

INCIPAL INVESTIGATOR: MAJ Thomas M. Baker, MC

PROFESSIONAL ASSISTANTS: COL Donald Kull, MC  
COL Frederick H. Stutz, MC  
LTC Dennis M. Lanier, MC

ORK UNIT NO: 81/106

#### TECHNICAL OBJECTIVES

to determine response rates of patients with previously untreated stage III and IV squamous cell CA of head and neck as well as response rates of similar patients who have had prior treatment and have local or systemic recurrence; to determine survival of previously untreated patients receiving preoperative or preradiotherapy chemotherapy and compare this survival to that of previously treated similar patients at MAMC or from the literature; to determine type and severity of adverse effects of the chemotherapy.

#### METHOD

Patients who meet the criteria as listed in the protocol will receive cis-platinum, 80 mg/M<sup>2</sup>, given with hydration and mannitol diuresis, followed by 5-FU, 1000 mg/M<sup>2</sup> by IV infusion, for 4 consecutive days. A second course is repeated in 3 weeks. After 2 courses, patients that have not had prior treatment would then be re-evaluated by radiotherapy and surgery for further therapy. In patients who have recurrent or metastatic disease, treatment is given every 3-4 weeks for as long as the tumor is controlled and the patient tolerates the side effects reasonably well.

#### PROGRESS

8/81 - 9/84) Seventeen (17) patients (4 with no prior treatment and 13 with extensive prior surgery and/or RT and/or chemotherapy) were treated with Cis-Platinum (100 mg/M<sup>2</sup>) followed by a 96 hour infusion of 5-FU (1000 mg/M<sup>2</sup>/d). Two of four patients with no prior treatment responded and 3 of 7 evaluable patients who had extensive prior treatment responded. When results of this study were compared to other studies using similar chemotherapy regimens, the conclusions were: very high response rates can be obtained in patients with no previous treatment; patients who achieve complete response to induction chemotherapy have prolonged survival over those who have less than a complete response; response rates in patients with recurrent and/or metastatic head and neck cancer are comparative to single agent chemotherapy rates; survival benefit using chemotherapy as either induction therapy or as salvage therapy remains to be proven. A paper was presented at the 4th Annual Current Concepts in Hematology/Medical Oncology Meeting, February 1984.

STATUS: (C)

DETAIL SHEETS  
FOR  
PROTOCOLS

DEPARTMENT OF MEDICINE

TITLE: The Impact of Notification of High-Risk Status on Patient Acceptance of Influenza Immunization, on Subsequent Patient Morbidity and Mortality, and on Total Health Care Costs

PRINCIPAL INVESTIGATOR: CPT Stephen A. Spaulding, MC

PROFESSIONAL ASSISTANTS: LTC James W. Higbee, MSC  
LTC David W. Roberts, MC  
CPT Cheryl Wofford, ANC  
SP5 Yenja Marcucci-Breshears, 91B20

WORK UNIT NO: 84/03

#### TECHNICAL OBJECTIVE

To test the hypothesis that actively seeking out and notifying those patients in a given practice population that are at high risk of complications from influenza results in a significantly higher percentage of high-risk patients accepting immunization when compared to a similar high-risk population not actively notified and to test the hypotheses that such notification results in decreased morbidity and mortality due to influenza and a significant reduction in overall health care costs to the military, when compared to the non-notified group.

#### METHOD

High-risk Family Practice (FP) patients will be identified by computer and randomized to either receive no notification of their high-risk status or being notified and recommending that they take the for influenza immunization. Immunizations will follow the standard procedure and nursing staff will check to see if the individual is on the list of subject patients. All study patients suspected of having influenza will have specimens taken for viral culture. Paired acute and convalescent sera will be obtained on these patients also, with H-I titers performed. Diagnoses of influenza, pneumonia, acute URI, viral illness, or acute bronchitis will be totaled monthly and at the conclusion of the study period for all study patients. All inpatient admissions of study patients will be screened for the diagnoses of influenza or pneumonia, and/or death. Hospitalizations will be tabulated for use in the final analysis. Data to be analyzed: percentage of group receiving immunization; requiring at least one clinic visit for the diagnosis studied; and with episodes of culture-proven influenza. For comparison with prior studies, the percentage of shot-receivers with subsequent clinical visits and lab evidence of influenzal infection will be compared to the non-receivers. Total health care costs in the notified group versus the non-notified group will be analyzed.

#### PROGRESS

Data is being collected. There has been no data analysis thus far.

STATUS: (O)

TITLE: Preventive Cardiology Demonstration and Education  
Research Grant

PRINCIPAL INVESTIGATOR: LTC David W. Roberts, MC

PROFESSIONAL ASSISTANTS: Daniel J. Erickson, M.D.  
William Neighbor, M.D.  
Robert L. Van Citters, M.D.  
Craig S. Scott, Ph.D.  
Steven C. Macdonald, M.P.H.  
Douglas C. Schaad, M.Ed.  
Marcia Hunt, B.A.

WORK UNIT NO: 84/69

#### TECHNICAL OBJECTIVE

The primary aim of the NHLBI Education/Demonstration Preventive Cardiology Project is introducing concepts and practice relating to primary prevention of coronary disease into the basic training of Family Practice residents in the University of Washington Family Practice Residency Network. The hypothesis to be tested is that a core curriculum of preventive cardiology integrated into the existing curriculum of a Family Practice residency training program will result in measurable modification of the attitudes, knowledge, and clinical practice of an intervention group of residents as compared to internal and external controls.

#### METHOD

All residents in the Madigan Family Practice Residency will be asked to test for their attitudes and knowledge of preventive cardiology. Following testing, a curriculum in preventive cardiology will be developed. This curriculum will be developed and administered in conjunction with the staff of the Department of Family Practice at Madigan. In an attempt to personalize the process of cardiovascular risk assessment, an individual cardiovascular risk profile will be made available to the residents. Clinical practice of preventive cardiology by residents will be measured by an audit of patient charts at twice yearly intervals. The audit will be conducted by Preventive Cardiology staff auditors from the University of Washington.

#### PROGRESS

Preliminary questionnaires were filled out by 15 of 16 resident physicians and returned to the University of Washington. Blood samples were obtained for lipid profiles and results were given to individual residents. Intervention in the form of three didactics on cardiovascular risk factors were presented and were moderately well attended. Labels and letters were prepared for retrospective chart audits.

STATUS: (O)

TITLE: Personnel Management Behaviors of Family Physicians

PRINCIPAL INVESTIGATOR: MAJ Matthew J. Gaspar, MC

PROFESSIONAL ASSISTANTS: None

WORK UNIT NO: 84/71

#### TECHNICAL OBJECTIVE

To explore the personnel management behaviors of family physicians based on relationship behavior, task behavior, and power.

#### METHOD

Three military family practice training centers will participate in this survey on personnel leadership skills. These institutions are not unique to the military but represent training programs newly developed, fairly well established, or in existence for an extended period of time. All practicing family physicians or residents on active duty will participate in a survey administered by trained personnel at Madigan AMC, Silas B. Hays Army Hospital, and Bremerton Naval Regional Medical Center. Because a small sample size is predicted, randomization will not occur. Proctored testing will take place during the practice board exams for Family Practice. The surveys will be administered to the staff physicians during faculty development seminars. Each physician will complete a demographic questionnaire to tabulate personal data, graduate education, business education or experience, and military experience. This will be followed by two surveys designed to assess behavioral aspects of personnel management. The first is the Power Perception Profile which quantifies power according to seven categories; coercive, connection, expert, information, legitimate, referent, and reward. This will be followed by the Leader Effectiveness and Adaptability Description which describes business management skills according to relationship behavior, task behavior, and leader effectiveness. This test measures three important aspects of personnel management that quantify a leader's perception of his interactions with his staff. The demographic data will be used to ascertain differences in management training among physicians. If marked differences exist, based on the number of courses taken by each physician, then first order statistics will determine whether training in management will bias the survey scores.

#### PROGRESS

The questionnaire was distributed to the three medical centers in October 1984. There has been a 50% return rate thus far. No statistical interpretations have been attempted.

STATUS: (0)

TITLE: A Comparison of Nystatin and 1% Hydrocortisone Cream to Nystatin Alone in the Treatment of Diaper Rashes

PRINCIPAL INVESTIGATOR: CPT Matthew J. Gaspar, MC

PROFESSIONAL ASSISTANTS: LTC James W. Higbee, MSC  
CPT Cheryl Wofford, ANC

WORK UNIT NO: 83/87

#### TECHNICAL OBJECTIVE

To test the hypothesis that the use of Nystatin cream and 1% Hydrocortisone cream significantly increases the rate of healing of simple diaper rashes when compared to Nystatin cream alone, 1% Hydrocortisone cream alone, or a placebo.

#### METHOD

Approximately 200 untreated infants of both sexes from one to 24 months of age will be evaluated as to the presence of a typical irritant type diaper dermatitis or candidiasis. Infants with seborrheic, atopic, impetiginous, or bacterial type lesions will be excluded from the study. All infants will be graded initially as to the type of rash isolated, the amount of erythema, and the location of rash. The rash will be cultured by gently scrubbing the margins of the rash with a swab moistened in transport media. The swab will be plated on Sabouraud agar for yeast and fungal growth and on McConkeys' and blood agar for gram negative and gram positive growth respectively. A questionnaire will then be completed. Mothers will then be issued in a blind, randomized fashion: water-based cream; Nystatin cream; 1% Hydrocortisone cream, or Nystatin cream with 1% Hydrocortisone cream. Mothers will be instructed to apply the cream evenly to the affected area four times daily. No other medications will be permitted during the study period. A reassessment will be made as to the effect of treatment 10 to 14 days later and the lesions or site of the lesions recultured. An instruction sheet concerning general skin care and diapering techniques will be explained and the parents will be given a follow-up appointment in 7 to 10 days. At the conclusion of the study, the patient code will be broken and statistical analysis performed using the Mann-Whitney test for non-parametric data.

#### PROGRESS

Data is still being collected. No statistical evaluation of the data has been performed thus far.

STATUS: (O)



DETAIL SHEETS  
FOR  
PROTOCOLS

DEPARTMENT OF FAMILY PRACTICE

TITLE: Evaluation of Fluosol in Treatment of Decompression Syndrome (DCS)

PRINCIPAL INVESTIGATOR: CPT Fred Volinsky, MC

PROFESSIONAL ASSISTANTS: COL Stephen R. Plymate, MC  
CPT Leonard M. Checchio

WORK UNIT NO: 84/82

#### TECHNICAL OBJECTIVE

To evaluate the effectiveness of Fluosol DA in increasing the survival rate of rats after experimentally-induced decompression syndrome.

#### METHOD

Ten rats will be used to perfect necessary techniques for anesthesia, catheterization, and compression/decompression.

Group I (control group - 20 rats) will be anesthetized and have an external jugular vein catheterized. The rats will then be placed in a portable compression chamber (1000 PSI) and pressurized at the rate of 100 ft/min to a pressure of 7 ATM, at which pressure they will remain for one hr. They will then be rapidly decompressed at 60 ft/min (3 min) to 1 ATM. They will be removed and placed in an oxygen chamber containing 100% oxygen. At this time, they will receive an IV infusion of Dextran, 50% estimated blood volume, over 4 mins. Survival rate will be recorded until 60 min post-decompression.

Group II (experimental - 20 rats) will be anesthetized, catheterized, compressed, and decompressed in the same manner as Group I. They will be placed in 100% oxygen and receive an IV infusion of Fluosol DA-50% of estimated blood volume over a 4-minute period. Survival rates will be recorded until 60 min.

Group III (Fluosol infusion controls - 20 rats) will be anesthetized and catheterized the same as Groups I and II and then placed in a chamber which will remain open with no pressurization. At one hr, they will be placed in a 100% oxygen environment and 50% of estimated blood volume of Fluosol will be infused over 4 min. Survival rate will be recorded until 60 min. This group will provide data as to the mortality of Fluosol infusion.

#### PROGRESS

Preliminary work was done on 15 rats to establish an LD<sub>50</sub> for the decompression model. Of 15 animals, 9 survived for >1 hr (60%) indicating establishment of an LD<sub>50</sub> with compression to 90 PSI for 45 min and decompression over a 2-min period. Five animals were utilized to practice internal jugular cutdowns with good success; IV boluses of 50% estimated blood volume were infused over a 1-min period with 24 hour survival of 100%. Project is now entering major experimental phase.

STATUS: (O)

TITLE: Clinical Application of Transcutaneous Oxygen Monitoring  
in Emergency Department Patients

PRINCIPAL INVESTIGATOR: CPT Peter A. Maningas, MC

PROFESSIONAL ASSISTANTS: MAJ Steven C. Dronen, MC  
CPT Carl E. Friedl, MC

WORK UNIT NO: 83/79

#### TECHNICAL OBJECTIVE

To evaluate the clinical usefulness of transcutaneous oxygen monitoring for the early recognition and management of hemorrhage and impending shock in emergency department patients.

#### METHOD

Acutely traumatized patients triaged to the major resuscitation area based on a high potential for major injury will be utilized. Patients with a prior history of cardiovascular or respiratory disease will be excluded from the study. Each patient will be evaluated and resuscitated appropriately per ATLS guidelines. A  $P_{tc}O_2$  electrode will be placed on the right deltoid after all standard prehospital resuscitative measures are completed. Each patient will undergo insertion of a CVP line for intermittent monitoring of central venous pressure. Fifteen minutes after electrode placement, an arterial blood gas will be obtained for measurement of  $PaO_2$ , pH, base deficit, and serum lactate.  $P_{tc}O_2$  will be continuously monitored. Blood pressure will be monitored each minute with a self-inflating cuff. CVP, pulse, and respirations will be recorded at each sampling period or as the patient's condition dictates. Additional sampling periods will occur at 15 minute intervals until transfer of the patient from the Emergency Department. Each patient will be followed for recognition of final outcome. Serum lactate levels will be measured photometrically by the modified Weil and Marbach method. Base deficit will be calculated using a formula based on the Siggard Andersen Nomogram. A minimum of 20 patients will be studied.  $P_{tc}O_2$  values will be compared by Student's t test to standard cardio-respiratory and biochemical parameters for the evaluation of hemorrhagic shock.

#### PROGRESS

(9/83 - 9/84) A pilot study in normal individuals indicated methodological and technical problems with this application of transcutaneous oxygen monitoring. This was reported in Am J Emer Med 2(2): 181-82, 1984. The principal investigator was transferred to LAIR before this study could be revised and initiated.

STATUS: (T)

## The Utility of Transcutaneous $PO_2$ and $PCO_2$ as Parameters in the Evaluation of Hemorrhage and Impending Shock - Maningas

period. After the total amount of blood is withdrawn, the dog will undergo a 30 min period of stabilization with two sampling periods 15 minutes apart. After the stabilization period, the dog will be reinfused at the same rate and with the same volume of blood withdrawn, minus the amount taken for blood gases and serum lactate levels. Sampling and recording will again be done during the last 30 sec of each 6 min period. At the end of reinfusion, the dog will undergo a one hr period of stabilization and observation. Repeat blood samples will be taken every 15 min during that time. At the end of the hour, all catheters will be removed, cutdown sites sutured, and the dog extubated after achieving an appropriate level of consciousness.

### PROGRESS

(9/83 - 11/83) In animals bled and subsequently reinfused 40% of their intravascular volume, it was demonstrated that a fall in  $PvO_2$  and PWP preceded a significant change in all other parameters;  $P_{tc}O_2$  values fell during hemorrhage despite a relatively stable  $PaO_2$ , reflecting a decrease in peripheral tissue perfusion; there was a significant reduction in  $P_{tc}O_2$  values prior to an abnormal elevation in serum lactate levels; and  $P_{tc}O_2$  and  $PvO_2$  values were most sensitive to changes in intravascular volume during reinfusion of shed blood. The investigators conclude that transcutaneous oxygen tension is a sensitive indicator of intravascular volume changes in the canine model. The ease of application, non-invasiveness, and portability make it ideal for use in medical clearing stations where the prognosis of the injured soldier is frequently determined. Further clinical study pertaining to its application in the military setting is recommended.

A paper was presented at five meetings, including selection for presentation at the 14th Army Science Conference, West Point, NY, June 1984. A paper has been submitted for consideration for publication to the American Journal of Emergency Medicine.

STATUS: (C)

TITLE: The Utility of Transcutaneous PO<sub>2</sub> and PCO<sub>2</sub> as Parameters  
in the Evaluation of Hemorrhage and Impending Shock

PRINCIPAL INVESTIGATOR: CPT Peter A. Maningas, MC

PROFESSIONAL ASSISTANTS: MAJ Steven C. Dronen, MC  
MAJ Stanley P. Liebenberg, VC  
CPT Karl E. Friedl, MSC

WORK UNIT NO: 83/78

#### TECHNICAL OBJECTIVE

To evaluate the usefulness of transcutaneous PO<sub>2</sub> and PCO<sub>2</sub> monitoring for the early diagnosis and management of hemorrhage and impending shock.

#### METHOD

Eight to ten dogs will be given water but no food 18-24 hr prior to experimentation. The dogs will be anesthetized 30 minutes prior to starting bleeding and maintained with IV administration of pentobarbital, 30 mg/kg of body weight, placed in the left lateral decubitus position, and tracheally intubated with a cuffed tube to maintain the airway. Cannulation of the external jugular vein with a Swan Ganz catheter and cannulation of the left femoral artery with PE205 will be done. Vascular pressures will be measured by quartz transducers and recorded on a multichannel oscillograph. The Swan Ganz catheter will allow constant monitoring of the central venous pressure and intermittent monitoring of the pulmonary capillary wedge pressure. Mixed venous blood gases will be obtained via the distal port of the Swan Ganz catheter.

Baseline arterial, venous, and mixed venous blood samples will be drawn prior to hemorrhage for determination of control pH, pCO<sub>2</sub>, base deficit, MVO<sub>2</sub>, Hgb, and serum lactate. Cardiac output will be determined by standard thermodilution technique. Simultaneous recording of P<sub>t</sub>CO<sub>2</sub> and P<sub>t</sub>CO<sub>2</sub> will be done at each sampling period. Base deficit will be calculated simultaneously using a formula based on the Siggard Andersen Nomogram. Serum lactate levels will be measured photometrically by the modified Marbach and Weil method. The volume of blood samples will remain constant and will be included in the total amount of blood withdrawn. The amount of blood to be withdrawn will be 40% of the calculated blood volume (approximately 35 cc/kg). This volume will be aspirated by syringe from the femoral artery catheter over a 30 min period with 1/5 of the total volume being withdrawn during the first 5 1/2 min of each 6 min period. Syringes will be changed and sequential arterial, venous, and mixed venous blood samples will be taken during the last 30 sec of each six min

TITLE: Effect of Fluosol DA on Massive Theophylline Intoxication  
in Rats

PRINCIPAL INVESTIGATOR: CPT Peter A. Maningas, MC

PROFESSIONAL ASSISTANTS: MAJ Steven C. Dronen, MC  
MAJ Stanley P. Liebenberg, VC  
CPT Karl E. Friedl, MSC

WORK UNIT NO: 83/71

#### TECHNICAL OBJECTIVE

To evaluate the effectiveness of partial exchange transfusion with Fluosol DA in reducing serum theophylline concentrations and mortality after massive intoxication in rats.

#### METHOD

Five groups (10 rats each) of male Sprague-Dawley rats weighing between 200-250 gms will be kept in an oxygen chamber filled with 100% O<sub>2</sub>. Three of the groups will receive partial exchange transfusion with Fluosol DA after intoxication with intravenous aminophylline and then transfused to a final hematocrit of 4%, 7%, and 10%, respectively. The last two groups will serve as controls for both the exchange procedure and for the theophylline intoxication. One group will undergo exchange without theophylline infusion and the other group will undergo theophylline infusion without exchange. All animals will have both the carotid artery and the tail vein cannulated. Fifty mg (250 mg/10 cc) aminophylline will be injected into the tail vein of each animal over 2 minutes, with a 15 minute stabilization period after injection. Those animals undergoing exchange transfusion will be bled through the carotid artery at a rate of 5 ml/kg/min. Infusion of Fluosol DA will occur through the tail vein at the same rate. Final hematocrits of 10%, 7%, and 4% will be obtained after approximately 15, 20, and 25 times the number of repetitions, respectively. Each of the Fluosol DA treated groups will also undergo supplemental infusion equal to 1.5 ml/100 gm body weight at one hour post-transfusion. Blood samples will be withdrawn from all groups every 5 minutes for measurement of hematocrit, fluorocrit, (in the transfused group) and serum theophylline. After transfusion, or the equivalent time period for the control group, catheters will be removed. The transfused groups will remain in 100% O<sub>2</sub> for the first 24 hours. Thereafter, they will be placed in 70% O<sub>2</sub>, 30% N<sub>2</sub> until the hematocrit returns to at least 20%, whereupon they will be returned to room air.

#### PROGRESS

(9/83 - 9/84) This project was discontinued after considerable preparation and equipment development because it was no longer clinically relevant with the disapproval by the FDA of human use of Fluosol.

STATUS: (T)

TITLE: Hemodynamic Responses to Application and Removal of Nitroglycerin Ointment in Normal Subjects

PRINCIPAL INVESTIGATOR: MAJ Kenneth Frumkin, MC

PROFESSIONAL ASSISTANTS: CPT Ted A. McMurry, MC

WORK UNIT NO: 82/17

#### TECHNICAL OBJECTIVE

To determine the temporal characteristics of the action of topically applied nitroglycerin on pulse and blood pressure volunteers. The onset of action, time required for maximal hemodynamic response, and the time for return to baseline values after the ointment has been removed will be measured.

#### METHOD

Sixteen (16) healthy male volunteer subjects with a normal blood pressure and pulse without orthostatic changes during the baseline phase of the experiment will be used. An automated Critikon blood pressure cuff and an automatic dental chair in the fully erect position will be used. Initially, orthostatic vital signs will be taken. Patients will then have pulse and blood pressure taken after being supine for two minutes and again after two minutes of standing. Those with a decrease in systolic blood pressure of 20, a decrease in diastolic blood pressure of 10, or a rise in pulse of >20 beats /minute will be excused from the study. Non-orthostatic patients will then sit erect in the chair and pulse and blood pressure will be recorded automatically by the device every two minutes for 14 minutes (baseline). Two inches (30 grams) of 2% nitroglycerin ointment will then be applied to a 53 cm<sup>2</sup> area at the left costal margin in the midclavicular line. Blood pressure and pulse will be recorded every two minutes by the machine and also by a physician. Symptomatic hypotension will be treated by Trendelenberg position and other standard means. After 40 minutes of continuous monitoring, one half of the patients (randomly assigned) will have the nitroglycerin paste completely wiped off with a clean terrycloth towel. Monitoring of these patients will continue for another 60 minutes. The control subjects will have the paste left on and will be monitored for the same period of time.

#### PROGRESS

(11/81 - 9/84) Postural hypotension could not be reliably reproduced with the nitroglycerin.

STATUS: (C)

## The Use of Naloxone in the Management of Hemorrhagic Shock - Dronen

Serum lactate levels will be measured photometrically by the modified Marbach and Weil method. The volume of blood samples will remain constant and will be included in the total amount of blood to be withdrawn. Forty percent (40%) of the calculated blood volume (approximately 35 cc/kg) will be aspirated by syringe from the femoral artery catheter over a 30 minute period with 1/5 of the total volume being withdrawn during the first 5 1/2 minutes of each six minute period. Syringes will be changed and sequential arterial, venous, and mixed venous blood samples will be taken during the last 30 seconds of each six minute period. After the total amount of blood is withdrawn, the dog will undergo a 60 minute period of stabilization with four sampling periods 15 minutes apart. The dog will be reinfused at the same rate and with the same volume of blood withdrawn, minus the amount taken for blood samples. At the end of reinfusion, the dog will undergo a one hour period of stabilization and observation. Repeat blood samples will be taken every 15 minutes during that time. At the end of the hour, all catheters will be removed, cutdown sites sutured, and the dog extubated after achieving the appropriate level of consciousness.

### PROGRESS

This study has been completed and the data are being analyzed.

STATUS: (C)



TITLE: Pilot Study for Treatment of Refractory Breast Cancer  
with Cis-Platinum and 5-Fluorouracil Infusion

PRINCIPAL INVESTIGATOR: MAJ Thomas Baker, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC Irwin B. Dabe, MC  
MAJ Howard Davidson, MC  
MAJ Timothy J. O'Rourke, MC  
CPT Michael D. Stone, MC

WORK UNIT NO: 84/57

#### TECHNICAL OBJECTIVES

To determine the anti-tumor activity of cis-platinum followed by continuous 4-day infusion of 5-FU given every 3 to 4 weeks in patients with metastatic carcinoma of the breast who have failed standard chemotherapy regimens utilizing response rate and duration of response to measure the activity and to determine the toxicity of the combination of 5-FU by continuous infusion over 4 days and high dose cis-platinum when given with hypertonic saline, magnesium, hydration, and aggressive antiemetic therapy.

#### METHOD

Following a 24-hr urine collection and simultaneous calculated creatinine clearance  $>60$  cc/min and adequate IV hydration with D5 and normal saline, cis-platinum,  $120 \text{ mg/M}^2$ , in 500 cc of 3% saline plus 500 CC solution of 20% mannitol and 3 grams of magnesium sulfate, will be given by IV infusion over 2 to 4 hours. This will be followed by continuous hydrating fluids. The day following cis-platinum chemotherapy, the patient will be started on 5-FU,  $1 \text{ mg/M}^2$ , by continuous IV infusion days 2 through 5. This will be followed by standard antiemetic regimens. This regimen will be repeated every three to four weeks as tolerated by the patient. Dosages will be modified as required by creatinine clearance and toxicity.

#### PROGRESS

Two patients have been entered in this study with no unexpected adverse toxicity or reactions in one patient and delayed nausea and vomiting, which subsequently subsided, in the second.

STATUS: (0)

TITLE: Gastric Ulcer Healing by Cimetidine, Sucralfate, or Combined Therapy: Speed of Healing, Safety, and Efficacy for Ulcers Resistant to Healing by One Agent Alone

PRINCIPAL INVESTIGATOR: MAJ V. Duane Bohman, MC

PROFESSIONAL ASSISTANTS: LTC Thomas F. O'Meara, MC  
MAJ Dennis I. Greenberg, MC  
MAJ Michael H. Walter, MC

WORK UNIT NO: 84/52

#### TECHNICAL OBJECTIVE

To determine if gastric ulcers can be healed faster and more completely with two anti-ulcer drugs than with one.

#### METHOD

Patients meeting the admission criteria will be entered no more than 72 hours after endoscopic confirmation of gastric ulceration and the absence of concomitant upper gastrointestinal disease. During the 12-week period of treatment, the patient will receive either sucralfate and cimetidine placebo, cimetidine and sucralfate placebo, or sucralfate and cimetidine on a double-blind, randomized basis. All drugs and placebos will be swallowed with water (without chewing) one hour before the three daily meals and at bedtime. Follow-up endoscopies will be scheduled for 2, 4, and 12 weeks to allow for accelerated early healing and assessment of complete healing rates. If after twelve weeks the ulcer has not healed and the patient received only one drug, he will be given both drugs for an extra four weeks and then rechecked. Any patient showing a significant worsening of gastric ulcer disease will be dropped from the study and placed on alternative treatment and will be considered a drug failure. Smoking and coffee and alcohol consumption will be recorded as well as age, sex, occupation, family history of ulcers, and gastric pH. The critical parameter of efficacy assessment will be complete healing.

#### PROGRESS

The study will begin as soon as the investigators receive the drugs and placebos.

STATUS: (0)

TITLE: Vinblastine - Continuous 5-Day Infusion in Refractory  
Advanced Solid Tumors

PRINCIPAL INVESTIGATOR: MAJ Alfred H. Chan, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC James E. Congdon, MC  
LTC Irwin B. Dabe, MC  
MAJ Thomas M. Baker, MC  
MAJ Lauren K. Colman, MC  
MAJ Howard Davidson, MC

WORK UNIT NO: 82/10

#### TECHNICAL OBJECTIVE

To determine the response rate and remission duration using Velban as a continuous IV infusion in patients with advanced solid tumors refractory to all effective forms of conventional treatment; and to define further the qualitative and quantitative toxicity of the continuous infusion of Velban.

#### METHOD

Since the response rate of these tumors at this stage to any particular agent or combination of agents has been dismal in the past, it would be meaningful, if a response rate of >15% can be established, to add this method to the existing regimens for the treatment of refractory solid tumors such as breast cancer, non-seminomatous testicular germ-cell cancer, small cell undifferentiated cancer of the lung, renal cell cancer, ovarian cancer, and lymphomas. This will be a single-armed study. The results will be compared with historical data whenever available. All patients registered on this study will be considered evaluable and be analyzed. Patients will be stratified according to tumor cell types. In the case of breast cancer, further substratification into ER+/- and pre- vs post-menopausal status will be carried out. Vinblastine will be given as a continuous infusion over five days every three weeks, provided there has been recovery from hematologic toxicity.

#### PROGRESS

(11/81 - 9/84) Sixteen patients were infused with vinblastine. Even though one patient had stable disease for 12 months and one patient had a partial response for nine months, all patients eventually relapsed. No life-threatening complications or neurotoxicity were seen; myelosuppression was usually mild; and nausea and vomiting were rare. The number of patients was too small for conclusive analysis. Though generally well tolerated, the treatment was not particularly as effective in this group of patients as reported elsewhere. The cost and inconvenience were substantial. A paper was presented at the 4th Annual Current Concepts in Hematology and Oncology Meeting, Feb 84.

STATUS: (C)

TITLE: To Develop In Vitro Cytotoxicity Against Human Colon Cancer Cells

PRINCIPAL INVESTIGATOR: MAJ Alfred H. Chan, MC

PROFESSIONAL ASSISTANTS: LTC Irwin B. Dabe, MC  
LTC James W. Higbee, MSC

WORK UNIT NO: 84/01

#### TECHNICAL OBJECTIVE

To determine the feasibility of developing and enhancing cytotoxicity by autologous lymphocytes against human colon cancer cells.

#### METHOD

This will be done utilizing the methods of mixed lymphocyte tumor culture and *in vitro* sensitization. Fifty ml of heparinized blood will be collected from the patient on the morning of surgery prior to pre-medication. Mononuclear cells will be isolated by floatation on Ficoll-Hypaque. T-cells and non-T cells will be separated by E-rosetting with AET sheep RBC's. The purified lymphocytes will be divided into portions LA, LB, LC, and LD. These will be cryopreserved and stored frozen for later use. Tumor tissue will be obtained from the fresh pathology specimen before fixation. Viable tumor cells will be separated by stepwise application of velocity and density sedimentation on gradient of Ficoll-Hypaque within 3 hours of tumor removal. Isolated, viable tumor cells will be incubated at 37°C in conditioned medium for 16 hours. Tumor cells will be divided into TA, TB, and TC. TA will be cryopreserved and stored frozen for later use as cytolytic targets. TB will be labelled with  $^{51}\text{Cr}$ . LB will be thawed and added to  $^{51}\text{Cr}$ -labelled TB for a 4-hour chromium release test to determine the baseline cytotoxicity of the unstimulated lymphocytes. Mitomycin C (25  $\mu\text{g}$ ) will be incubated with TC. After washing, this will be placed with thawed LC in mixed lymphocyte tumor culture (MLTC) and incubated at 37°C and 5%  $\text{CO}_2$  for 5 days. LD will be placed in culture without tumor cells to serve as MLTC control and incubated at 37°C and 5%  $\text{CO}_2$  for five days. One portion of the cells harvested from the TC/LD mixture will be used to determine the degree of proliferation with tritiated thymidine; a second portion of these cells will be tested *in vitro* for cytotoxicity against thawed and  $^{51}\text{Cr}$ -labelled target tumor cells (TA) by the 4-hour  $^{51}\text{Cr}$  release method; and a third portion will be harvested and allowed to interact with Interleukin-2 for seven days. The cells from the Interleukin-2 portion will be harvested and tested *in vitro* for cytotoxicity against more of the thawed and labelled target tumor cells by the 4-hour  $^{51}\text{Cr}$  release method. The extent of cytotoxicity of each step will be calculated. Specificity controls: a. allogenic peripheral blood lymphocytes b. allogenic tumor cells. Autokilling controls: autologous T cells: a. frozen thawed; b. fresh post-operation.

To Develop In Vitro Cytotoxicity Against Human Colon Cancer  
Cells - Chan

PROGRESS

(10/83 - 7/84) Specimens from three patients were tested. Ample cells were recovered, but the tumor cells failed to remain viable after separation, probably because of a delay in processing the specimen. During the T-cell expansion of the second specimen, a heavy fungal contamination occurred. The addition of Fungizone failed to decontaminate and the experiment had to be aborted at the half-way point; therefore the decision was made to add Fungizone to the medium at the beginning for future testing.

The third specimen yielded only 40 million total from 50 ml of blood. The centrifuge rate may have been suboptimal. The efficacy of the AET SRBC to rosette T-cells should be confirmed from time to time. A great deal of difficulty was encountered in rendering the tumor cells a true single-cell suspension and keeping it so after cryopreservation. Consultations were made with experienced cell culture researchers who emphasized that adequately mincing the tissue and then passing the cells through the 40-micron nylon mesh are mandatory. They also recommended that 0.02% EDTA be added to the conditioning medium during the initial steps of tumor cell separation to enhance the removal of calcium ions responsible for intercellular adhesion. Also, a much longer treatment time with the enzymes was recommended.

When using the method of unit gravity velocity gradient to separate the tumor cells from the non-tumor cells, the question of homogeneity remains. Perhaps the cell sorter can eventually overcome this problem. Physicians at the Stem Cell Assay Lab in Seattle have expressed interest in collaborating to start a stem cell culture at MAMC. This might serve to overcome the problem of viability of the tumor cells after cryopreservation. Cryopreservation of both T-cells and non-T-cells with 20% DMSO in liquid nitrogen consistently yielded 50-70% recovery of viable cells upon thawing.

Cytotoxicity tests with the <sup>51</sup>Cr release method were performed before and after *in vitro* sensitization with mixed T-lymphocyte and tumor cell cultures. The results reflected no significant enhancement in cytotoxic ability, indicating poor sensitization.

The result of the T-cell expansion was biphasic and disappointing overall. After an initial phase of rapid replication, the cells failed to expand further. The Fungizone in the culture medium might have played an important role or the preservation of potency of the Interleukin-2 as well as that of the fetal calf sera after prolonged freezing. The technical aspect of medium changing might also be refined to a more gentle manner to prevent inadvertent cell loss through overly vigorous suctioning. Finally, the condition of the incubator must always be closely monitored.

The investigators conclude that it is feasible to perform this type of experiments at MAMC once the technical difficulties are overcome.

STATUS: (C)

TITLE: Conjunctival Biopsy in the Diagnosis of Sarcoidosis

PRINCIPAL INVESTIGATOR: LTC Henry D. Covelli, MC

PROFESSIONAL ASSISTANTS: COL Stanley Sollie, MC  
COL Stanley Allison, MC  
LTC Jerome Beekman, MC  
MAJ Bruce Bellin, MC  
MAJ Leslie P. Fox, MC  
MAJ Richard Robinson, MC  
MAJ Barry Weled, MC  
CPT Myron Whitehead, MC

WORK UNIT NO: 79/85

#### TECHNICAL OBJECTIVE

To evaluate the usefulness of conjunctival biopsy as a primary means of diagnosing sarcoidosis.

#### METHOD

Patients with a tentative diagnosis of sarcoidosis based on accepted clinical, radiologic, and biochemical criteria will have baseline evaluations to include chest x-ray, PPD and anergy battery, angiotension converting enzyme level, erythrocyte sedimentation rate, arterial blood gases, and pulmonary function tests to assess disease activity. These patients will undergo slit lamp examination. Patients with conjunctival follicles will have those follicles biopsied and those with normal appearing conjunctiva will have random biopsies. Tissue will be examined histologically for noncaseating epithelioid granulomata with hematoxylin and eosin stain. If granulomata are observed, the specimen will be examined utilizing polarized light microscopy and stained and examined for acid fast bacilli and fungi. If no granulomata are observed, no further examination will be done. Patients will then be evaluated with transbronchial lung biopsy. Data on the field from transbronchial biopsy will be compared to that from conjunctival biopsy. In addition, disease activity as manifest by serum ACE level will be correlated with biopsy positivity.

#### PROGRESS

Results indicate a biopsy rate (+) for noncaseating granulomas consistent with sarcoidosis in 85% of tranbronchial biopsies, 67% of minor salivary gland biopsies, and 35% of conjunctival biopsies. These findings mirror previously reported studies. In only one case did conjunctival biopsy yield a result when transbronchial history was negative. The investigators subsequently looked at an additional five patients to see if doing multiple conjunctival biopsies would increase yield, which it did not.

STATUS: (C)

TITLE: Evaluation of High Dose vs Low Dose Corticosteroid in the Treatment of Acute Bronchospasm

PRINCIPAL INVESTIGATOR: LTC Henry D. Covelli, MC

PROFESSIONAL ASSISTANTS: COL J. Waylon Black, MC  
COL Bruce L. Fariss, MC  
LTC Gary Treece, MC  
MAJ Arthur R. Knodel, MC  
CPT James Wallingford, MC

WORK UNIT NO: 82/64

#### TECHNICAL OBJECTIVES

To evaluate the optimal dose of corticosteroids used in the treatment of acute exacerbations of bronchospasm and to assess the difference in the duration of adrenal suppression between low and high dose corticosteroid therapy.

#### METHOD

Approximately 50 patients hospitalized for an acute exacerbation of bronchospasm from either chronic obstructive lung disease or asthma will be evaluated in a double blind randomized trial. Treatment will consist of the usual therapeutic measures of IV aminophylline and orally inhaled bronchodilators. Then one of four corticosteroid regimens will be used. Regimen 1: 125 mg of IV methylprednisolone (MP) q 6 hrs x 3 days with a weaning oral prednisone dose of 60 mg x 3 days, 40 mg x 3 days, and 20 mg x 3 days. Regimen 2: 125 mg of IV MP q 6 hrs x 3 days with a weaning dose of oral prednisone of 30 mg x 3 days, 20 mg x 3 days, and 10 mg x 3 days. Regimen 3: 125 mg MP q day x 3 days, then a weaning dose of oral prednisone of 60 mg x 3 days, 40 mg x 3 days, and 20 mg x 3 days. Regimen IV: 125 mg MP q day x 3 days, then a weaning dose of oral prednisone of 30 mg x 3 days, 20 mg x 3 days, and 10 mg x 3 days. A placebo of IV glucose will be given q 6 hrs to patients receiving regimens 3 and 4. Routine studies such as eosinophil counts and peak expiratory flow rates (spirometry) will be performed during this time. After discharge, patients will be evaluated with a Cortrosyn stimulation test one or two weeks after discontinuing a weaning dose of oral prednisone. If the Cortrosyn stimulation test is abnormal, a repeat study will be performed weekly until it normal.

#### PROGRESS

(8/82 - 9/84) Sixty subjects were entered. No difference was found between the high and low dose steroids in resolving pulmonary symptoms. A paper was presented at the Carl Templeton Annual Allergy-Chest Conference, FAMC, January 1984.

STATUS: (C)

TITLE: Evaluation of Androgen Levels in Patients with Chronic Obstructive Pulmonary Disease and Sleep Apnea

PRINCIPAL INVESTIGATOR: LTC Henry D. Covelli, MC

PROFESSIONAL ASSISTANTS: COL Bruce L. Fariss, MC  
COL Stephen R. Plymate, MC  
MAJ Arthur R. Knodel, MC  
MAJ Robert W. Taylor, MC  
Marueeen Nuccio, M.D., Amer Lake V.A. Hosp  
Leonard Sarff, RRT, DAC

WORK UNIT NO: 83/77

#### TECHNICAL OBJECTIVE

To compare patients with obstructive lung disease without sleep apnea to patients with carbon dioxide retention but no evidence of sleep apnea and to patients with a diagnosis of sleep-apnea. Also to evaluate the side effects of exogenous testosterone in patients receiving this agent for urological problems.

#### METHOD

This study will evaluate three different groups of male patients in the following categories:

Group I: Fifteen male patients with obstructive lung disease without CO<sub>2</sub> retention. Hormonal levels will be evaluated by measurement of total serum testosterone, free serum testosterone, estradiol, 17-OH progesterone, and progesterone. Sleep apnea studies will be performed at the VA Medical Center.

Group II: Fifteen male patients with obstructive lung disease with CO<sub>2</sub> retention. Hormone level analysis and sleep apnea studies as in Group I.

Group III: Fifteen male patients who have a diagnosis of sleep-apnea and have previously had sleep studies will be evaluated with serum hormonal analysis.

Data will be analyzed using analysis of variance.

#### PROGRESS

(9/83 - 9/84) Three patients were entered. The study was terminated due to the departure of Drs. Covelli and Fariss.

STATUS: (T)



TITLE: 5-Azacytadine in Acute Leukemia

PRINCIPAL INVESTIGATOR: LTC Irwin Dabe, MC

PROFESSIONAL ASSISTANTS: COL Friedrich Stutz, MC  
MAJ Lauren Colman, MC

WORK UNIT NO: 80/19

#### TECHNICAL OBJECTIVE

To examine the efficacy of 5-Azacytadine in patients with acute leukemia refractory to conventional therapy.

#### METHOD

5-Azacytadine will be given in a dose of 300 mg/M<sup>2</sup>/day for 5 days in three or four divided doses each day. Courses will be repeated every three weeks unless there is earlier evidence of recovery from myelotoxicity. If bone marrow cellularity is less than 20% at three weeks from the last course, chemotherapy will be withheld until marrow cellularity exceeds 20%. Dosages for the next course will then be reduced by one third. If there is no improvement in the bone marrow after the initial course, the drug dosage for the second course will be increased by one third.

#### PROGRESS

Two patients were treated on this study in FY 80 with very little response to the drugs, followed by death from uncontrolled leukemia.

No patients were entered during FY 81 or FY 82.

One patient was entered during FY 83 and developed a temperature spike to 105° after the first dose. Her temperature remained normal for the next two doses, but the patient developed cellulitis of the lower right leg which resolved upon discontinuation of the drug. The patient was restarted on 5-azacytadine, but PB blasts reappeared by day 20 confirmed by bone marrow aspirate. 5-azacytadine was discontinued and the patient later expired.

No patients were entered in FY 84.

STATUS: (O)

TITLE: The Effects of Hyperthyroidism on Serum Zinc, Iron, and Copper Values in the Sprague-Dawley Rat

PRINCIPAL INVESTIGATOR: MAJ Michael Fincher, MC

PROFESSIONAL ASSISTANTS: COL Bruce Fariss, MC  
COL Stephen Plymate, MC  
LTC Gary Treece, MC  
MAJ James Little, MSC

WORK UNIT NO: 83/27

#### TECHNICAL OBJECTIVE

To determine the effect of thyroxine on serum copper, zinc, iron, ferritin, and ceruloplasmin in Sprague-Dawley rats and to correlate these findings with reported observations in human patients with thyrotoxicosis.

#### METHOD

Thirty (30) male Sprague-Dawley rats, approximately 8 weeks of age, weighing between 200 and 250 gm will be allowed access to food and water *ad libitum*. Control and experimental rats will be injected intraperitoneally daily with either 1.0 ml saline (control) or 30 gm L-thyroxine (T<sub>4</sub>) in saline (experimental). Each group will consist of fifteen rats and on days 0, 14, 28, and 56 both control and experimental groups will be anesthetized with halothane and bled by cardiac puncture. Serum copper, zinc, and iron will be measured by atomic absorption. Serum total T<sub>4</sub>, free T<sub>4</sub>, ceruloplasmin, and ferritin will be measured by radio-immunoassay. Results of control and experimental groups will be compared by the unpaired Student's t Test.

#### PROGRESS

(11/82 - 6/84) Serum T<sub>4</sub>, T<sub>3</sub>, copper, and iron were measured in male and female rats injected daily with levothyroxine. Serum T<sub>3</sub> and T<sub>4</sub> rose variably in the experimental animals. Serum copper tended to fall with the administration of levothyroxine.

PRESENTATION: Fincher, ME, Little, JS, Plymate, SR and Fariss, BL: Effect of Hyperthyroidism in the Rat on Body Weight, Serum Copper, and Serum Iron. Presented to Society of Uniformed Endocrinologists Meeting, San Antonio, TX, 7-8 June 1983.

STATUS: (C)

TITLE: Therapy of the Costochondralgia Syndrome - A Randomized  
Controlled Therapeutic Study

PRINCIPAL INVESTIGATOR: MAJ James D. Fitz, MC

PROFESSIONAL ASSISTANTS: LTC Michael J. Weaver, MC  
CPT Donald R. Skillman, MC

WORK UNIT NO: 83/38

#### TECHNICAL OBJECTIVE

To evaluate the efficacy, when treating anterior chest wall pain of an oral analgesic; an injection of anesthetic/steroid suspension; a combination of oral analgesic and the anesthetic/steroid injection; and a placebo.

#### METHOD

Inclusion criteria will be anterior chest wall pain which is replicated by palpation or pressure upon costochondral junctions. Exclusion criteria will be allergy or other reaction to local anesthetics, steroids, or aspirin or underlying cardiopulmonary or esophageal conditions which in the opinion of the evaluating physician account for the pain syndrome.

Approximately 100 patients will be randomized into five treatment groups. Group A will receive an injection of a combination of local anesthetic (Marcaine Hcl®) plus steroid (Aristospan®) in addition to oral Ecotrin. Group B will receive an injection of the anesthetic plus steroid in addition to an oral placebo. Group C will receive Ecotrin. Group D will receive an injection of normal saline in addition to an oral placebo. Group E will receive an oral placebo only. Patients will be given a diary in which to record daily assessment of pain and will return the diary on the 14th day following injection. An objective evaluation of tenderness will be performed by the use of "Dolorometer" prior to injection, 30 minutes following injection, and then on days 1, 2, 3, 7, and 14. Patients in each group will be given an oral non-anti-inflammatory analgesic for PRN use.

#### PROGRESS

(1/83 - 5/83) A total of sixteen patients was entered into the study. Dr. Michael Weaver (co-investigator) was transferred to WRAMC in May 1984. He will become the principal investigator on this protocol and will continue to collect patients once approval has been received from the IRB at WRAMC.

STATUS: Transferred

TITLE: Prospective Evaluation of Clinical, X-Ray, Histologic,  
Scintigraphic and Microbiologic Characteristics of  
Diabetic Feet

PRINCIPAL INVESTIGATOR: MAJ John Gnann, MC

PROFESSIONAL ASSISTANT: LTC Thomas Parr, MC  
MAJ Shannon Harrison, MC

WORK UNIT NO: 83/51

#### TECHNICAL OBJECTIVE

to correlate specific x-ray, scintigraphic, clinical and microbiologic characteristics with each other and with the histology of the diseased diabetic foot so clinicians may better manage their patients.

#### METHOD

This will be a blinded, multicenter study with 30 patients entered study-wide.

Eligibility: Any diabetic patient whose physician for any reason has decided with the patient that amputation of the foot is indicated except for urgency of surgery which would preclude diagnostic studies and pregnancy. It is not necessary for a patient to have probable infection to be entered into the study; they will be a natural control group.

The following diagnostic procedures will be performed: radiograph of the foot to be amputated in the dorsal and lateral views; bone scan of the part to be amputated; two intra-operative trephine biopsies of any radiolucent areas or areas of elevated periosteum (one will be fixed for histology and one will be cultured for anaerobes and aerobes); neurologic examination of the foot to include vibration, proprioception reflexes to pinprick and light touch; (e) manual palpation of the D. pedis and P. tibial pulses; and aerobic and anaerobic cultures of drainage from sinuses. Doppler determination is important but not required.

Data Analysis: The histology will be compared to radiographs and scans and the results of the trephine biopsy. The sensitivity and specificity of the trephine and the radiologic studies will be determined relative to the histology. The clinical worksheets will be evaluated to see if there are any clinical characteristics which are peculiar to bone infections.

#### PROGRESS

8/83 - 9/84) This study has been terminated due to a lack of patients (none entered at MAMC).

STATUS: (T)

TITLE: Western Washington Randomized Trial of Intravenous Streptokinase in Acute Myocardial Infarction

PRINCIPAL INVESTIGATOR: COL John C. Hill, MC

PROFESSIONAL ASSISTANTS: COL W. Theodore Steudel, MC  
LTC Roger F. Chamusco, MC  
LTC John W. Kirk, MC  
MAJ Stanley E. Pearson, MC

WORK UNIT NO: 84/12

#### TECHNICAL OBJECTIVE

To determine if high dose infusion of Streptokinase administered early in the course of a myocardial infarction will reduce hospital mortality when compared to conventional CCU care.

#### METHOD

Patients with a clinical and electrocardiographic diagnosis of acute, transmural myocardial infarction of <6 hours duration will be randomized to control or streptokinase treatment group. Patients will be stratified according to the time of onset of symptoms and location of myocardial infarction. Controls will receive conventional therapy and IV heparin. The treatment group will receive streptokinase, 1,500,000 units in 250 ml of D<sub>5</sub>W, as a 1-hr IV infusion. They will then receive full dose IV heparin anticoagulation. CPK or CPKMB isoenzymes will be drawn every 4 hours during the first 24 hours. These CPK curves will be used to define the occurrence of acute myocardial infarction and to give evidence of reperfusion. A gated blood pool radionuclide angiogram will be obtained at 0-48 hours after randomization to assess early left ventricular function. A coronary angiogram and contrast left ventriculogram will be performed prior to discharge at 7-14 days. If contrast ventriculography is declined by the patient, a second isotope radionuclide ventriculogram will be obtained. At 30-45 days, subjects will have a tomographic 201-Thallium quantitative myocardial perfusion study performed. At the same visit, each patient will have a standard radionuclide blood pool study for global EF, as well as a tomographic blood pool study for analysis of regional EF. Each patient's vital status will be determined at 6 months and one year. After 100 subjects have been studied, an independent monitor will analyze the data for significant findings before entering more patients.

#### PROGRESS

Patients are still being entered. No adverse reactions have been reported.

LE: Clinical Evaluation of Siemens Dual Chamber Pacemaker

PRINCIPAL INVESTIGATOR: COL John C. Hill, MC

PROFESSIONAL ASSISTANTS: COL W. Theodore Steudel, MC  
LTC Roger F. Chamusco, MC  
LTC John W. Kirk, MC  
LTC Manuel Martinez, MC  
MAJ Stanley E. Pearson, MC

UK UNIT NO: 84/41

#### TECHNICAL OBJECTIVE

demonstrate the effectiveness and safety of the Siemens Pulse Generator 674, an AV-sequential DDD pulse generator, which contains certain functions, programmability, and specifications available on currently marketed units.

#### METHOD

Approximately six patients will be selected for dual chamber pacing according to the established criteria. At the time of implantation, the following parameters will be measured and recorded: atrial and ventricular sensing and pacing thresholds, retrograde A-V conduction time, documentation of satisfactory atrial and ventricular pacing. Prior to hospital discharge and four weeks, the following tests will be obtained: atrial and ventricular stimulation thresholds, documentation of pulse generator rates, and post implantation chest x-rays. Evaluation of physiologic functioning of the unit will be demonstrated by exercise testing. Determinations will be repeated at three, six and twelve months after implantation with the exception of the chest x-ray. Patients will be compared with previous patients implanted with pacemakers without certain features of the Siemens unit in regard to programmability, pacing thresholds, and pulse generator impulse versatility.

#### PROGRESS

(84 - 9/84) There was a delay in obtaining an IND number for this protocol due to inaccurate information submitted to the drug company. The principal investigator retired from the service before approval could be received; therefore the protocol is terminated.

STATUS: (T)

AD-A154 970

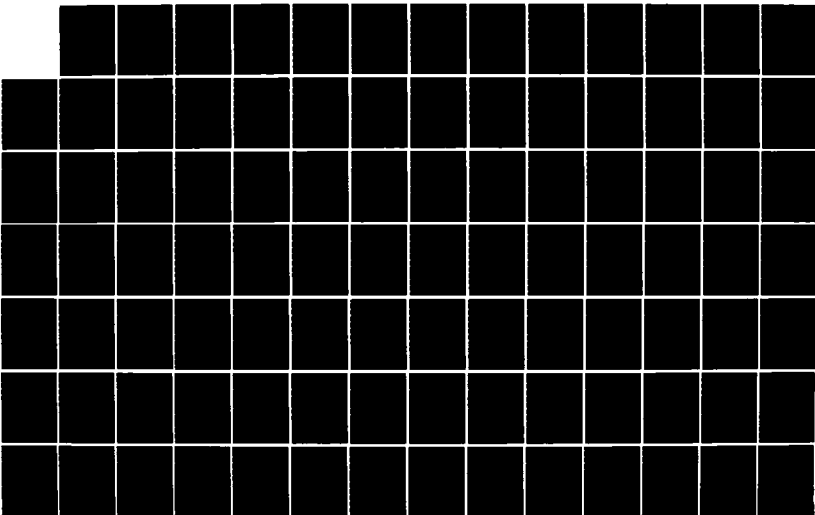
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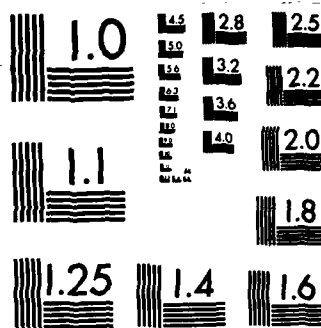
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TITLE: Regulation and Kinetics of Fatty Acid Activation in Liver and Skeletal Muscle

PRINCIPAL INVESTIGATOR: MAJ Robert E. Jones, MC

PROFESSIONAL ASSISTANTS: COL Bruce L. Fariss, MC  
COL Stephen R. Plymate, MC  
LTC Gary L. Treece, MC  
MAJ James S. Little, MSC

WORK UNIT NO: 83/09

#### TECHNICAL OBJECTIVE

To explore the cellular and hormonal mechanisms which control the rate of mitochondrial fatty acid activation.

#### METHOD

Thirty male rats (6-8 in each phase) will be the source of the enzyme used. After sacrifice by decapitation, mitochondria will be prepared from the quadriceps femoris muscle group and liver using differential centrifugation or a gradient. Ligase activity will be measured using a modification of the radiochemical millipore filter assay proposed by Polokoff and Bell. Approximately 0.08  $\mu$ Ci of (3H)-coenzyme A will be used per assay. The initial phase of the study will consist of re-establishing the basic assay and kinetic parameters of the enzyme from each tissue and preparative methodology. The second phase will involve examining the effects of various known intracellular mediators and cytoplasmic fractions on enzymatic rate. The third phase will analyze the action of insulin and glucagon on ligase activity by preincubating these hormones with crude tissue homogenates or other cellular components and mitochondria. The main emphasis will be on the effects on palmitic acid kinetics by holding all other reactants and cofactors at saturating concentrations while varying palmitate levels. Each experiment will be run in a paired fashion with tissue from each animal serving as its own control. Enzymatic rates will be normalized to nanomoles palmitoyl CoA formed/minute/mg protein. Maximal velocity will be experimentally determined and Michaelis constants will be calculated using Cleland's hyperbolic best-fit formulation. Statistical analysis will be performed using a paired t test or analysis of variance.

#### PROGRESS

(10/82 - 9/84) Liver and muscle tissue were obtained from control rats, thyrotoxic rats, aged rats, and fasted rats, and stored at -70°C awaiting measurement of ligase activity. Due to time restraints the investigators were unable to continue work on the protocol for some time. During this period of time a better model for studying palmitic acid activation was identified; therefore the protocol has been terminated.

STATUS: (T)

TITLE: Studies on Fatty Acid Activation in Spermatozoa:  
Kinetics and Localization

PRINCIPAL INVESTIGATOR: MAJ Robert E. Jones, MC

PROFESSIONAL ASSISTANTS: COL Bruce L. Fariss, MC  
COL Stephen R. Plymate, MC

WORK UNIT NO: 83/81

#### TECHNICAL OBJECTIVE

To define the kinetic characteristics and cellular localization of the enzyme system responsible for the initiation of saturated fatty acid metabolism in spermatozoa.

#### METHOD

Normal human semen samples will be used to establish a ligase assay. Ligase activity will be measured using a sensitive radio-ligand/millipore filter procedure that utilizes (3H)-coenzyme A as the radioactive trace. Approximately 0.2 microcuries of (3H) will be present in each individual assay. The samples will be centrifuged at 2800g for 10 minutes at room temperature, the seminal plasma supernatant will be discarded, and the sperm pellet will be resuspended in an isotonic buffer. This sperm mixture will be recentrifuged and washed twice prior to use. After the final centrifugation, the pellet will be diluted in a potassium enriched buffer to achieve a sperm density of 200 million per ml. The assay mixture will contain palmitic acid, ATP, Mg++ and CoASH and will be initiated by the addition of the washed sperm preparation. Time and protein dependency curves will be run to determine the length of incubation needed to achieve first order kinetics in the measurement of initial velocities. Both Lineweaver-Burk plots and hyperbolic best-fit will be used to calculate approximate Km values for each substrate. Temperature, pH curves, and rates with alternate substrates will also be run. Enzyme location/latency will be determined by assaying separate cell fractions prepared by sonication and differential centrifugation of the isolated sperm. The effects of sulfhydryl reagents, albumin, and detergents will be studied to assist in estimation of latency.

#### PROGRESS

Kinetic studies on sperm ligase have been essentially completed. The technical problems associated with the determination of the Km for palmitic acid have been overcome ( $K_m \text{ Pa} = 4.4 \mu\text{M}$ ); however, studies to localize ligase have been unrewarding because the procedures used to separate sperm heads and tails (sonication, n-butylamine, and alkali) also destroy ligase activity. A paper has been submitted for publication in the Journal of Andrology and also for presentation at the 3rd International Congress of Andrology.

STATUS: (O)

TITLE: *In Vitro* Characterization of a LH-TSH Secreting Pituitary  
Macroadenoma

PRINCIPAL INVESTIGATOR: MAJ Robert E. Jones, MC

PROFESSIONAL ASSISTANTS: COL Bruce L. Fariss, MC  
COL Stephen R. Plymate, MC  
LTC James W. Higbee, MSC  
Mina G. Garrison, M.T., DAC

WORK UNIT NO: 84/83

#### TECHNICAL OBJECTIVE

To establish a human TSH secreting pituitary adenoma in tissue culture in order to study the TSH secretory response to a variety of secretagogues.

#### METHOD

Adequate tissue was obtained at surgery for histologic studies. The additional tumor will be placed in sterile media, consisting of 2.5% collagenase, 5% trypsin and 0.2 µg/ml DNase (in Hanks balanced salt solution) for 80 minutes to achieve cell disposal. Fetal calf serum will be added as a non-specific enzyme inhibitor, and the cells will be gently resuspended by manual pipetting, washed in media 199 and plated in 10 ml wells (≈0.5-1 million cells/well). The cells will be cultured in media 199 fortified with 10% fetal calf sera, Hanks salts and streptomycin/penicillin to retard bacterial growth. The tissue will be incubated at 37°C using a humidified atmosphere consisting of 5% CO<sub>2</sub> and 95% air. Media will be changed every two days and will be saved for baseline hormone determinations. Twenty-four hours prior to testing with LHRH, TRH, and somatostatin, the fortified media will be replaced with serumless 199. The hypothalamic hormones will be introduced in nanomolar quantities and the culture will be returned to the incubator. After 24 hours, the media will be removed for assay (LH, TSH, FSH, growth hormone, and two subunits) and exchanged for the fortified 199. The effects of calcium will be studied by performing similar experiments in calcium free Hanks or by co-incubating the cells with verapamil.

#### PROGRESS

The pituitary tumor was maintained in tissue culture for nearly forty days. Preliminary assays of the spent media showed an LH (RIA) of 19.2 mIU/ml and TSH of 6.8 µIU/ml on day 10 and an undetectable TSH on day 30. The completion of assays is pending the arrival of reagents and standards.

STATUS: (O)

**TITLE:** A Comparison of Thallium Stress Testing and Cardiac Pacing Stress Testing in the Preoperative Evaluation of Patients Undergoing Abdominal Aortic Aneurysmectomy and/or Aorto-femoral Revascularization

**PRINCIPAL INVESTIGATOR:** LTC John W. Kirk, MC

**PROFESSIONAL ASSISTANTS:** COL Charles Andersen, MC  
COL Stanton Brown, MC

**WORK UNIT NO:** 84/80

#### TECHNICAL OBJECTIVE

To determine the utility of treadmill stress testing with thallium perfusion imaging and cardiac pacing stress testing in the preoperative evaluation of patients with evidence of heart disease who are scheduled to undergo major vascular surgery involving the abdominal aorta, the iliac arteries, and/or the femoral arteries.

#### METHOD

Each subject will undergo treadmill stress testing followed by thallium perfusion imaging. A week later, each patient will undergo a right atrial pacing stress test followed by selective left and right coronary angiography and contrast left ventriculography from a brachial artery. If contrast left ventriculography is not performed or is of suboptimal technical quality, a blood pool radionuclide angiogram will be obtained within 48 hours. Patients will be followed through induction of anesthesia and the post-operative period for cardiac complications, and the vital status will be determined at one and six months. Coronary arteriography will be employed as the gold standard to determine the sensitivities, predictive values, specificities, and accuracies of these two diagnostic tests in identifying coronary artery disease, particularly left main and severe three vessel coronary disease. In order to determine the ultimate value of any of these tests in increasing operative survival and reducing perioperative complications, surgical results in these patients will be compared with those of a similar group of patients who underwent the same type of surgery without such extensive preoperative evaluation.

#### PROGRESS

New study. No patients enrolled in FY 84.

**STATUS:** (O)

**TITLE: Face Mask CPAP for Prevention of Post-Op Atelectasis**

**PRINCIPAL INVESTIGATOR: MAJ Arthur R. Knodel, MC**

**PROFESSIONAL ASSISTANTS: COL Waylon J. Black, MC  
LTC Henry D. Covelli, MC  
LTC Michael Moon, MC  
CPT Richard Dearman, MC  
CPT William Weaver, MC  
Donald Winfrey, DAC**

**WORK UNIT NO: 82/72**

#### TECHNICAL OBJECTIVE

To evaluate the usefulness of continuous positive airway pressure (CPAP) delivered by a face mask as a prophylactic measure in the prevention of post-operative pulmonary atelectasis.

#### METHOD

One hundred patients undergoing elective abdominal or thoracic surgery will be studied. Patients with acute pulmonary diseases, including ARDS, CHF, and pneumonia, diagnosed immediately post-operatively, will be excluded. No intubated patient will be included in the study. Patients will be randomly assigned to one of three groups: control group - conservative therapy of cough-deep-breath (no device); incentive spirometry (3) CPAP by mask at a level of 10. Pre-operative evaluation will include pulmonary function test, arterial blood gas, and chest x-ray. Four hours post-operatively all of these studies will be repeated. The patient will then be given a treatment followed in 15-30 minutes by repeat pulmonary function test and arterial blood gas. During waking hours the patient will receive the treatment for 15 minutes every four hours. Pulmonary function test, arterial blood gas, and chest x-ray will be done at 24, 48, and 72 hours. At that time the study will be completed.

#### PROGRESS

(9/82 - 9/84) Forty-two subjects were studied. The decrease in FVC for the incentive spirometry (IS) group was significantly less ( $p < .05$ ) than for the cough-deep-breath (CDB) group on Day 1. Otherwise, there was no difference in the three groups for absolute or relative changes in FVC, FEV<sub>1</sub>, or A-a gradient. Clinical atelectasis occurred least frequently in the CPAP group (5/15), but was not statistically different from the patients on CDB (5/12) or IS (7/14). A paper was presented at the American Thoracic Society Meeting, Miami, May 1984. The results were also published in the American Review of Respiratory Diseases 129: A110, 1984.

**STATUS: (C)**

**TITLE:** Effect of Cigarette Smoking on Plasma Carboxyhemoglobin  
and on the Diffusion Capacity of Carbon Monoxide

**PRINCIPAL INVESTIGATOR:** CPT Perry R. Lloyd, MC

**PROFESSIONAL ASSISTANTS:** Leonard Sarff, DAC  
Dan Mould, DAC

**WORK NO:** 83/66

#### TECHNICAL OBJECTIVE

To evaluate the effect of cigarette smoking on the diffusing capacity of carbon monoxide ( $D_{CO}$ ) and on the carboxyhemoglobin (COHb) levels in cigarette smokers.

#### METHOD

Twenty to thirty consenting cigarette smokers (outpatient alert men and women >18 years of age) will be asked not to smoke after midnight before the day of testing. Routine PFT,  $D_{CO}$ ,  $PO_2$ , COHb, Hb, height, and weight will be obtained in the morning before testing. Subjects will then chain smoke high carbon monoxide-producing cigarettes as noted in the Federal Trade Commission's March 1983 report. This will be done in a room ventilated by a wall fan. The number of cigarettes smoked by each subject will not be controlled, but the number of cigarettes smoked by each subject will be noted and results will be correlated according to the number of cigarettes smoked. Repeat  $D_{CO}$ ,  $PO_2$ , and COHb will be performed and a hemoglobin will be obtained by a hemogram. An arterial puncture of the radial artery will be performed both before and after the smoking period with collection of 3-5 cc of blood each time.

#### PROGRESS

(7/83 - 6/84) Sixteen patients were enrolled. However, due to a lack of technical support (personnel shortage) for the pulmonary function tests, the study had to be terminated.

**STATUS:** (C)

TITLE: Arrhythmias with Bronchodilators

PRINCIPAL INVESTIGATOR: CPT Perry R. Lloyd, MC

PROFESSIONAL ASSISTANTS: COL John C. Hill, MC  
Anselmo Rodriquez, DAC

WORK UNIT NO: 83/76

#### TECHNICAL OBJECTIVE

To evaluate the cardiac rhythm effects of bronchodilators in chronic obstructive pulmonary disease patients.

#### METHOD

Twenty (20) non-steroid dependent chronic obstructive pulmonary disease outpatients with an  $FEV_1/FVC < 55\%$  substantiated by two sequential PFT's, who maintain theophylline levels at 10-20  $\mu\text{gm/ml}$  at 6 to 8 hours after their morning dose, and who use aerosolized metaproterenol or albuterol, will carry 2-channel Holter monitors on three occasions for 24 hr: once with no beta-2 agonist, once with albuterol, and once with metaproterenol. They will be asked to record times and amounts of drugs, caffeine, and alcohol used and to use no new drug therapies for two weeks prior to the initial Holter monitoring and until after completion of all three monitorings. Prior to entry patients will have a cardiopulmonary exam and an EEG. An electronic electrographic scanner will be used to record rhythm abnormalities by the time of day in the standard format for interpretation. Two weeks prior to the initial testing while on a stable regimen, the patients will have theophylline levels determined. Potassium levels and an ear oximetry will be done prior to the first Holter monitoring: a level of 3.5-5.0 K+ mEq/dl and an ear oximetry indicating saturation of  $>90\%$  will be required. Peak flow rates will be measured before and after the Holter monitoring. Patients using beta-blocker therapy or any antiarrhythmic medications or oral steroids up to two weeks prior to and through the testing, erythromycin and any of its congeners, or any other antibiotics for airways disease will be excluded, as will patients with histories of congestive heart failure, myocardial ischemia, myocardial infarction, or ECG's suggesting ischemia or infarction.

#### PROGRESS

(9/83 - 6/84) Thirty-three patients were entered in this protocol. Results of the study have not been received by this office; however a paper has been accepted for presentation at the Annual Meeting of the American College of Chest Physicians in October 1984 and at the American College of Physicians/Department of the Army Internal Medicine Conference in October 1984.

STATUS: (C)

**TITLE:** Determination of a Possible Association Between Migraine Headaches and Attention Deficit Disorders in Children

**PRINCIPAL INVESTIGATOR:** MAJ Joseph P. McCarty, MC

**PROFESSIONAL ASSISTANTS:** Staff, Department of Pediatrics

**WORK UNIT NO:** 84/54

#### TECHNICAL OBJECTIVE

To determine if there is an unusually high incidence of migraine headaches in children with attention deficit disorders.

#### METHOD

For purposes of this study, migraine will constitute any headache with three or more of the following characteristics: throbbing, presence of an aura before the headache, unilateral pain, history of sleep walking or motion sickness, nausea or vomiting with the headache, or positive family history of migraine headaches.

Attention deficit disorder syndrome is defined as a syndrome of developmentally inappropriate inattention and impulsivity. Hyperactivity may be an associated feature but is not required for diagnosis.

A questionnaire will be given to all new patients referred to the Pediatric Clinic for evaluation of attention deficit disorder. This questionnaire will be reviewed by the examining physician, and he will complete an additional questionnaire. The same questionnaire will be utilized with patients who come to the Pediatric Clinic for routine school physicals. This group will serve as a control group. From these questionnaires, the number of patients with attention deficit disorder and migraine can be compared to the number of controls with migraine. As attention deficit disorder is seen primarily in males, the controls will be adjusted by sex and age to match the study group. It is estimated that approximately 100 patients in the study group and 200 patients in the control group will provide more than sufficient numbers for statistical significance.

#### PROGRESS

Approximately 100 control subjects have been entered with an incidence of migraines of .095. The number of study patients enrolled to date is insufficient for any analysis. The investigators will continue to enroll both study and control subjects.

**STATUS:** (O)



**TITLE: Tegretol® vs Phenytoin in Epileptic Children Under Six Years of Age**

**PRINCIPAL INVESTIGATOR: MAJ Joseph P. McCarty, MC**

**PROFESSIONAL ASSISTANTS: COL Carl A. Plonsky, MC**

**WORK UNIT NO: 84/55**

#### TECHNICAL OBJECTIVE

To compare the safety and efficacy of Tegretol and phenytoin as initial therapy in the treatment of generalized tonic-clonic seizures, partial seizures, and mixed seizures in children under six years of age.

#### METHOD

This will be a multi-center, randomized, parallel group, double-blind study comparing Tegretol and phenytoin. Blinding will be accomplished by use of a coinvestigator who will follow anti-convulsant serum levels and convey to the investigator whether they are low, therapeutic, or high. This will assist the investigator in determining the dosage of the anticonvulsant. Success will be defined as achieving a complete control of epilepsy with no occurrence of seizures. Efficacy of the drugs will be measured from the time therapeutic levels are attained.

Length of study: 76 weeks

Length of study per patient: 24 weeks (10 visits)

Number of patients: a minimum of 20 completed patients at each institution.

#### PROGRESS

(5/84 - 9/84) This project was never implemented. CIBA-GEIGY's deadline for patient enrollment could not be met because of the continued delays regarding funding approval, and the protocol had to be terminated.

**STATUS: (T)**

TITLE: High Dose Intravenous Gammaglobulin for Chronic  
Idiopathic Thrombocytopenic Purpura

PRINCIPAL INVESTIGATOR: MAJ Timothy J. O'Rourke, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC James Congdon, MC  
LTC Irwin B. Dabe, MC  
MAJ Thomas M. Baker, MC  
MAJ Alfred H. Chan, MC  
MAJ Howard Davidson, MC

WORK NO: 83/62

#### TECHNICAL OBJECTIVES

To evaluate the efficacy of human immunoglobulin in treatment of chronic idiopathic thrombocytopenic purpura (ITP) that has not responded to conventional therapy and to observe changes in the serum proteins pertinent to the immune system during therapy.

#### METHOD

This is to be a multicenter study among the Army MEDDACS. It is anticipated that 5-6 patients will be needed to begin a valid study. At MAMC, 1-2 patients per year are expected. All patients with ITP documented by a compatible bone marrow picture and absence of secondary etiologies will be eligible. This will be restricted to patients who have failed conventional therapy, have severe thrombocytopenia and/or have spontaneous hemorrhage. Patients who are otherwise being treated but have life-threatening hemorrhage or who must undergo surgery may be included at the discretion of the study coordinator.

Patients will be treated with 0.4 mg/kg/day I.V. gammaglobulin as an infusion on each of five successive days. Should a response occur, weekly or biweekly maintenance will be continued. If the response is prolonged, the frequency will be lengthened and ultimately stopped.

#### PROGRESS

Two patients have been entered; one in FY 83 and another in FY 84. Neither responded to treatment with high dose intravenous gamma-globulin.

STATUS: (O)

TITLE: CT Scanning and Myelography in the Diagnosis of Metastasis to the Axial Skeleton

PRINCIPAL INVESTIGATOR: MAJ Timothy O'Rourke, MC

PROFESSIONAL ASSISTANTS: COL John Redmond, MC  
MAJ Howard Davidson, MC  
MAJ William Fill, MC

WORK UNIT NO: 84/02

#### TECHNICAL OBJECTIVES

To examine the utility of CT scanning compared to plain radiographs in the diagnosis of metastatic disease of the spine; to investigate the role of CT Metrizamide myelography in detection of subclinical compromise of the spinal canal; and to observe the course of patients with subclinical compromise of the spinal canal evaluated in this way.

#### METHOD

Patients enrolled in this study must have: (a) normal neurologic exam, or at least absence of neurologic findings attributable to spinal cord or nerve root compression and (b) either abnormal bone scan with new findings in a patient with known metastatic or high risk primary malignancy or multiple myeloma or other neoplasms with high frequency of false negative bone scan who have back pain. Patients will be evaluated as outlined below:

Carcinoma patients with a positive bone scan and a positive x-ray will go on to a CT/metrizamide myelogram and treatment; those with a negative x-ray will go on to a CT and then (if the CT is positive) to the CT/metrizamide myelogram and treatment (if the CT is negative no further testing); those with a positive bone scan and a negative x-ray and CT will have no further testing.

Patients with multiple Myeloma and back pain will follow the same schedule through x-ray, CT, and CT/metrizamide myelogram.

Treatment will be at the discretion of the treating physician and radiotherapist. Follow-up will be as appropriate for the individual patients. Bone scan will be repeated as needed for new symptoms or every three to four months in the absence of new symptoms. CT scans and CT metrizamide myelograms will be repeated as needed.

#### PROGRESS

Thirty-five patients with high risk primary or known metastatic cancer, normal neurological exam and new bone scan abnormality in the axial spine were evaluated. The investigators conclude that this algorithm allowed the detection of benign disease, the presence and extent of bone metastasis, and a high incidence of cord compression. Information was obtained without complications and allowed precise therapeutic planning. More patients will be studied. A paper has been accepted for the Army Hematology/Oncology Meeting in October 1984.

STATUS: (O)

TITLE: The Role of Phosphate in the Anemia of Chronic Renal Failure.

PRINCIPAL INVESTIGATOR: COL Poong S. Shim, MC

PROFESSIONAL ASSISTANTS: COL Stephen R. Plymate, MC  
MAJ Edward Lelonek, MC  
CPT Wayne R. Heaton, MC  
CPT Douglas R. Hough, MC

WORK UNIT NO: 82/60

#### TECHNICAL OBJECTIVE

To study the role of serum phosphate levels in the anemia of chronic renal failure patients on maintenance hemodialysis. It has been proposed that parathyroid hormone is a uremic toxin. The contribution of secondary hyperparathyroidism to the anemia of hemodialysis patients will be studied. The elevated serum phosphate levels and parathyroid hormone levels of secondary hyperparathyroidism are expected to be reduced with low phosphate diet, oral phosphate binders, and Rocaltrol. The response of the anemia to the treatment of the secondary hyperparathyroidism will be evaluated.

#### METHOD

Subjects undergoing hemodialysis and patients with chronic renal failure and evidence of secondary hyperparathyroidism will be studied. Patients with chronic constipation or documented non-compliance will be excluded. Pre-study bloodwork for each patient will include SMA-20, CBC, serum iron/TIBC, serum ferritin, folate, B-12, and PTH level. Radiographs of the hands for evidence of secondary hyperparathyroidism will be done. All patients will receive written and verbal instructions describing the study and the need for compliance with a low phosphate diet, oral phosphate binders, and Rocaltrol, a potent metabolite of vitamin D given to manage the hypocalcemia and reduce the elevated parathyroid hormone levels. Serum phosphate and calcium levels will be monitored monthly during the study; the calcium phosphate product will be maintained at  $<70$ . Alucaps or aluminum hydroxide will be given to control serum phosphate levels. Patients will be examined every two weeks for adverse side effects. The study duration will be for a minimum of six months. At the end of the study, all the pre-study bloodwork will be repeated. Radiographs will be repeated only for patients with pre-study evidence of bone cysts or subperiosteal resorption. Each patient will serve as his own control with pre-study values compared with study values using the Student's t Test. Also each individual will be compared with the group.

#### PROGRESS

(6/82 - 9/84 No patients were entered on this protocol due to the reassignment of the investigators from the Nephrology Service. Due to this lack of professional personnel, COL Shim has requested that the protocol be terminated.

STATUS: (T)

TITLE: Efficacy of Weekly Pulse Methotrexate in the Treatment of Rheumatoid Arthritis: A Double Blind Crossover Study

PRINCIPAL INVESTIGATOR: MAJ James Yovanoff, MC

PROFESSIONAL ASSISTANTS: MAJ Robert C. Hays, MC

WORK UNIT NO: 84/38

#### TECHNICAL OBJECTIVES

Part I: To evaluate the effectiveness of weekly pulse methotrexate therapy to control the activity of rheumatoid arthritis who have failed therapy with gold salt and D-penicillamine. Part II: To evaluate the potential of long-term weekly pulse methotrexate therapy to halt or decrease the progression of destructive changes of the articular cartilage and periarticular bone. Part III: To evaluate the potential for hepatic toxicity of weekly pulse methotrexate. In addition, careful evaluation of longitudinal evaluations of hepatic morphology will allow for close monitoring of potential changes to prevent progression of methotrexate-induced fibrosis to cirrhosis.

#### METHOD

This will be a multicenter study. Part I will be a double blind crossover study of weekly pulse methotrexate therapy compared to a placebo. Patients will be randomized to the methotrexate or the placebo and treated at increasing dose levels until a response is obtained for a 13-week period. Patients then will be crossed over to the opposite agent and treated in a similar manner for the second 13-week period. Patients will be clinically followed for the duration of the study by a single physician blinded as to the medication being received. Activity of disease, response to therapy, and drug toxicity will be evaluated.

PART II: Patients will have x-ray evaluation of affected joints at the initiation of therapy with methotrexate and at six month intervals for the duration of therapy. Patients treated with methotrexate but not included in Part I of the study will be included in Part II if the route of administration and dosage range are the same and they meet inclusion criteria. X-ray films will be blinded, graded, and evaluated for potential progression of disease.

PART III: Biochemical liver function studies will be monitored monthly. Liver biopsy will be performed at initiation of therapy and at appropriate intervals as indicated. When not contraindicated, laparoscopic directed liver biopsy will be performed to aid in the sensitivity of detection of potential liver injury. Percutaneous liver biopsy will be performed if standard contraindications to laparoscopy exist. Data on hepatic toxicity if noted will be compared to the patient's clinical status, concurrent medications, other evidence of toxicity, and methotrexate dosages.

#### PROGRESS

Two patients were entered in Part II of the study and begun on weekly methotrexate. They were judged to have an adequate response and have continued on the medication for four months. There have been no liver function abnormalities to date.

STATUS: (O)

TITLE: Nifedipine and Hydrochlorothiazide in the Control of Hypertension

PRINCIPAL INVESTIGATOR: LTC Michael J. Weaver, MC

PROFESSIONAL ASSISTANTS: LTC Gary Treece, MC  
MAJ Marvin Hayami, MC  
CPT Daniel Knodel, MC  
CPT Gregory Schlepp, MC  
1LT Scott Martin, MSC

WORK UNIT NO: 84/09

#### TECHNICAL OBJECTIVE

To test the effect of nifedipine alone, furosemide alone, hydrochlorothiazide alone, nifedipine + hydrochlorothiazide, and nifedipine + furosemide for the control of hypertension.

#### METHOD

Entry criteria: essential hypertension alone; essential hypertension plus non-insulin diabetes mellitus; or isolated systolic hypertension. Exclusion criteria: other significant medical problems or on other medications (other than anti-hypertensive drugs and oral hypoglycemic agents), and suspected renovascular or other secondary causes of hypertension.

Baseline evaluation: history, physical exam, BUN, fasting glucose, creatinine, electrolytes, calcium, urinalysis, and urine electrolytes, calcium and creatinine; EKG and chest x-ray will be if none has been done within the last year.

Method: Patients on a single anti-hypertensive drug will be withdrawn and their blood pressure will be allowed to stabilize for one to two weeks. This will be a double blind, cross-over study with patients sequentially randomized into the five groups listed in the objective section (placebo will be added to the drugs used alone). An initial period of two weeks will be required to achieve stabilization, followed by a four week follow-up phase. At the end of each period, patients will be crossed-over to a new study regimen. At the end of each study, the baseline values will be repeated. Each subject will be crossed over to each group unless some detrimental effect is found.

Outcome Assessment: Systolic and diastolic blood pressure will be recorded in the sitting and standing positions on each clinic visit. The mean arterial blood pressure will be compared between groups for evidence of drug effect. Serum potassium, glucose, drug tolerance, and compliance will also be assessed.

#### PROGRESS

(10/83 - 5/84) The principal investigator was unable to obtain the necessary drugs and matched placebos before reassignment; therefore the protocol had to be terminated.

STATUS: (T)

**TITLE:** Evaluation of Radiation Therapy in the Management of  
Endoscopically Visible Tumors of the Lung

**PRINCIPAL INVESTIGATOR:** CPT James Wallingford, MC

**PROFESSIONAL ASSISTANTS:** COL Donald Kull, MC  
LTC Jerome Beekman, MC  
LTC Henry D. Covelli, MC  
MAJ Arthur R. Knodel, MC  
MAJ Barry Weled, MC

**WORK UNIT NO:** 79/77

#### TECHNICAL OBJECTIVE

To evaluate in a prospective manner the utility of using radiation therapy to decrease tumor size in obstructing carcinomas of the lung.

#### METHOD

A minimum of 15 patients with carcinoma of the lung will be evaluated in the usual manner. If the patient is a non-operable candidate with endoscopically visible lesions, he will receive radiation therapy and/or chemotherapy in the usual manner with reassessment of pulmonary functions, arterial blood gases, and fiberoptic bronchoscopy approximately one month after radiation and again approximately six months after radiation. The parameters used to evaluate progression or regression of disease will be changing roentgenographic effect (collapse, atelectasis) in the area of involvement, alteration of pulmonary function and arterial blood gases, and changing luminal size of obstructing lesions as noted by fiberoptic bronchoscopy. Repeat biopsy results from prior areas of involvement will also be used to assess therapeutic results.

#### PROGRESS

Thirty-three patients (four entered during FY 84) were entered on this protocol with no adverse effects. It was found that radiotherapy significantly reduced bronchoscopically visible obstructing carcinoma in a majority of patients. Dyspnea was relieved or stabilized regardless of objective response of the tumor. Chest x-ray appears adequate to follow the patient clinically with pulmonary function tests adding little helpful information. Improvement in flows and volume can only be anticipated in patients with mainstem obstruction. Post obstructive pneumonias were not prevented by palliative radiotherapy. A paper is being prepared for submission for publication.

**STATUS:** (O)

TITLE: Liver Function Tests in the Normal Postpartum Female

PRINCIPAL INVESTIGATOR: CPT Amy M. Tsuchida, MC

PROFESSIONAL ASSISTANTS: MAJ V. Duane Bohman, MC  
MAJ Arthur S. Maslow, MC  
MAJ Thomas F. O'Meara, MC  
MAJ Arthur Schipul, MC  
CPT Stephen H. Koopmeiners, MC  
CPT Paul F. McKenney, MC

WORK UNIT NO: 83/32

#### TECHNICAL OBJECTIVE

To determine when liver function tests return to normal levels after uncomplicated pregnancy and delivery.

#### METHOD

One hundred third trimester patients with uncomplicated courses will be interviewed on age, parity, alcohol intake, and medications, including contraceptives. Information on lactation will be included after delivery. Patients with a history of hepatobiliary disease, renal disease, or diabetes will be excluded. Blood samples will be obtained at 36-40 weeks, labor, one week postpartum, two weeks postpartum if prior liver function tests were abnormal, and at 6 weeks postpartum if prior liver function tests were abnormal. Bilirubin, LDH, SGOT, GGT, alkaline phosphatase, serum protein, and albumin will be tested on a routine SMAC.

#### PROGRESS

(1/83 - 9/84) No patients have been entered. Both Dr. McKinney and Dr. Maslow were reassigned (FY 83) and Dr. Amy Tsuchida agreeded to assume responsibility for this protocol (Oct 84); however, due to TDY and other commitments she was unable to commence work on the protocol. Therefore, the protocol has been terminated.

STATUS: (T)



TITLE: Evaluation of Cyclosporin for Graves' Ophthalmopathy

PRINCIPAL INVESTIGATOR: LTC Gary L. Treece, MC

PROFESSIONAL ASSISTANTS: None

WORK UNIT NO: 84/84

#### TECHNICAL OBJECTIVE

To evaluate the effect of Cyclosporin in a patient with moderately severe Graves' ophthalmopathy responsive to prednisone but complicated by clinically significant Cushing's syndrome.

#### METHOD

The drug is to be used outside of the already approved protocol (entitled "Treatment of Graves' Ophthalmopathy with Cyclosporin" #84/40, LTC Treece) as the patient is unable to be incorporated into protocol due to lack of pretreatment baseline data.

The patient to be treated is a 31 y.o. white female with treated hypothyroidism secondary to <sup>131</sup>I treatment for Graves' disease X 2. She has congenital macular degeneration OS. In November 1983 the patient presented with pain and inflammation<sup>OD</sup> that was treated with a course of antibiotics. Her symptoms and signs recurred in March 1984 with pain, periorbital edema, proptosis OD, (treated with 100 ng prednisone which resulted in a prompt remission). She is biochemically euthyroid. CT of orbits revealed thickening of the right lateral rectus. Her symptoms of pain and sign of inflammation recur when prednisone is tapered and local steroid injections are not effective. The patient has developed a Cushingoid body habitus. Irradiation of orbits and surgery are relatively contraindicated due to her unilateral vision.

The plan is to treat her with 5-10 ng/kg Cyclosporin orally q.d. and taper the prednisone dosage. Baseline TFT, CBC, and SMA-20, Cyclosporin and B<sub>2</sub>-microglobulin levels, CT of the orbits and trough, and complete ophthalmologic exam will be repeated at monthly intervals until stable. The patient will be treated with the drug for at least three months tapering the dose to the lowest effective dose or until significant toxicity ensues. If the drug proves to be efficacious, it will be continued indefinitely.

#### PROGRESS

Cyclosporin was administered to the patient on a trial basis as the physician's best choice of treatment. The patient was unable to tolerate the side effects. No data were collected. The protocol was terminated.

STATUS: (T)

TITLE: Treatment of Graves' Ophthalmopathy with Cyclosporin

PRINCIPAL INVESTIGATOR: LTC Gary L. Treece, MC

PROFESSIONAL ASSISTANTS: COL Stanley Allison, MC  
COL Francis G. LaPianan, MC  
COL Leonard Wartofsky, MC  
MAJ Robert E. Jones, MC  
CPT Andrew Ahmann, MC

WORK UNIT NO: 84/40

#### TECHNICAL OBJECTIVE

To assess the efficacy of Cyclosporin treatment on the ophthalmopathy of Graves' disease.

#### METHOD

This will be a collaborative study with the Endocrine Services at the other MEDCEN's. The study will be composed of a random cross-over design comparing cyclosporin treatment to the most commonly employed current therapy, high dose oral prednisone. Since responses tend to be seen rapidly the drugs will each be administered for three weeks. Each patient's response to one drug will be compared to his own response to the other drug. A total of 20 patients will be evaluated initially with random alternating allocation to either Group A or Group B:

- Group A: (1) prednisone, 40 mg, T.I.D. x three weeks  
(2) full evaluation of response  
(3) cyclosporin 5-10 mg/kg/day x three weeks

Group B: Reverse order of Group A.

Clinical assessment will be weekly with ophthalmopathy index and T<sub>4</sub>, T<sub>3</sub>, etc, at 0, 4, 6, 9, and 12 weeks. TRH will be done at 0, 4, and 9 weeks, and cyclosporin or prednisone levels will be done at 2, 3, 4, 7, 8, and 9 weeks.

#### PROGRESS

One patient has been entered on the protocol. The patient developed epigastric pain, vomiting, facial flushing, and ear and jaw pain while taking 10 mg/kg cyclosporine for two days. A smaller dose gave milder symptoms, which were still intolerant to the patient. A UGI showed a pyloric channel ulcer, and the patient was taken off the study. One other patient was identified as a candidate for cyclosporine but did not qualify as she was on prednisone when initially seen in the Endocrine Clinic (see Protocol #84/84 by LTC Treece).

STATUS: (O)

The Effect of Rapid, Short Term Blood Glucose Control on Leukocyte Function in Diabetic Patients - Treece

PROGRESS

Work on this protocol continues at the stage of attempting to validate a workable leukocyte function test assay. The pour plate technique of determining phagocytic and bactericidal function of leukocytes incubated with *S. aureus* has temporarily been abandoned due to the inability to obtain consistent results. At present a counting of viable vs nonviable intracellular bacteria is being performed. Meanwhile, the results of a similar protocol were published in J Clin Pathol 37:1029-31, 1984 (Influence of Glycaemic Normalization by an Artificial Pancreas on Phagocytes and Bactericidal Function of Granulocytes in Insulin Dependent Diabetic Patients) by a group from Bordeaux Cedex, France. The results were as anticipated in that granulocytes from diabetes patients showed a decreased ability to absorb and kill *S. Aureus*, and improvement (but not correction) in these functions was observed after 36 hr of normoglycemia. In light of this published study of a similar protocol, the difficulties in establishing a leukocyte function test, and the limited technician support available to conduct this portocol, the principal investigator will need to reveiw the feasibility of continuing work on the protocol.

STATUS: (O)

**TITLE:** The Effect of Rapid, Short Term Blood Glucose Control on Leukocyte Function in Diabetic Patients

**PRINCIPAL INVESTIGATOR:** LTC Gary L. Treece, MC

**PROFESSIONAL ASSISTANTS:** COL Bruce L. Fariss, MC  
COL Stephen R. Plymate, MC  
LTC James Higbee, MSC  
MAJ Michael Fincher, MC  
MAJ Robert E. Jones, MC

**WORK UNIT NO:** 83/37

#### TECHNICAL OBJECTIVE

To study the effect on leukocyte function testing *in vitro* of rapid and sustained normalization of blood glucose levels in poorly controlled diabetic patients. Blood glucose control is to be accomplished using the Biostator - GCIIIS (Glucose Controlled Insulin Infusion System).

#### METHOD

Six Type I and six Type II adult, non-pregnant, non-infected, poorly controlled diabetic patients will be the subjects for this study. They will not be taking antibiotics, glucocorticoids or other drugs known to affect hormonal or cellular immunity or leukocyte or bacterial activity. Any diabetic drug therapy will be discontinued during the period of Biostator Control.

After admission to the hospital, each patient will be connected to the Biostator, initially in Monitor Only mode, and blood for base-line fasting blood glucose, insulin, SMA-20, CBC, blood culture, triglycerides, Hg A<sub>1</sub>C, and leukocyte function will be drawn. The Biostator will then be programmed to lower the blood glucose to 100 mg % and maintain the blood glucose at 100 mg % for 24-72 hours with the patient ingesting a weight maintaining diet divided into sevenths (2/7, 2/7, 2/7, 1/7). Blood for leukocyte function will be drawn at 2, 4, and 6 hours after normalization of blood sugar and every 6 hours thereafter. Should it be determined that leukocytic function can be altered with less than 6 hours of blood glucose normalization, the Biostator will be programmed to raise the blood glucose to 200 mg % 12 hours prior to termination of the study period. After 6 hours of a sustained blood glucose of 200 mg %, blood for leukocytic function will again be drawn. Then the blood glucose will be raised to 300 mg % for an additional 6 hours followed by repeat leukocytic function testing. Biostator control of the patient's blood glucose will then be terminated and the patient placed back on prior treatment regimen.

**TITLE:** The Utility of Urinary Free Cortisol to Monitor Replacement Therapy for Adrenal Insufficiency

**PRINCIPAL INVESTIGATOR:** LTC Gary L. Treece, MC

**PROFESSIONAL ASSISTANTS:** COL Bruce Fariss, MC  
MAJ Robert Jackson, MC

**WORK UNIT NO:** 82/05

#### TECHNICAL OBJECTIVE

To evaluate the possible usefulness of monitoring urinary free cortisol as an objective parameter of therapy that may avoid both under and over medicating patients with chronic adrenal insufficiency.

#### METHOD

Ten euthyroid patients with spontaneous or surgically induced adrenal insufficiency will be evaluated. Patients taking Aldactone will not be included unless it can be withdrawn. Patient involvement will be divided into three parts. During all three parts, the dose of any mineralocorticoid will not be altered. Patients having been on previous maintenance dose of glucocorticoid for at least three days and free of acute illness will be asked to collect two consecutive 24<sup>hr</sup> urines for free cortisol, 17 LH corticosteroids, and creatinine. A fasting plasma cortisol, an ACTH level, and a 2-hr post-dose cortisol will be drawn on one of the days that the urine is being collected. Patients will then be asked to take an amount of glucocorticoid, orally, equivalent to 50% of their maintenance dosage for seven days, after which blood and urine will be obtained. If a difference should be found in any of the parameters between patients taking hydrocortisone vs cortisone, several patients will be asked to switch to an equivalent amounts of the other drug in the maintenance dosage for seven days after which blood and urine will be obtained. If a difference should be found in any of the parameters between patients taking mineralocorticoid and those not taking such a drug, several patients on mineralocorticoid will be asked to discontinue the drug for 7 days and be restudied. Also, several patients not taking mineralocorticoid will be asked to take Florinef 0.1 mg/day orally for 7 days and be restudied as above. At the conclusion of the study, the patients will be given their maintenance dose and type of drug(s) unless otherwise clinically indicated.

#### PROGRESS

No subjects have been entered since FY 82 as patients with primary adrenal insufficiency were unavailable. Patient samples will be analyzed when 6-10 patients have been studied. Other studies cited in the literature indicate the need for the information sought in this study.

**STATUS:** (O)

**TITLE:** The Effect of Nephrosis on Treated Hypothyroidism

**PRINCIPAL INVESTIGATOR:** LTC Gary L. Treece, MC

**PROFESSIONAL ASSISTANTS:** COL Bruce L. Fariss, MC  
COL Stanton Brown, MC  
COL Stephen R. Plymate, MC  
COL Poong S. Shim, MC  
MAJ Lawrence Agodoa, MC  
MAJ Edward Lelonek, MC  
MAJ James W. Little, MSC  
MAJ Louis N. Pangaro, MC  
MAJ David Turnbull, MSC

**WORK UNIT NO:** 81/56

#### TECHNICAL OBJECTIVE

To document an anticipated increased dosage requirement for patients with treated hypothyroidism who develop the nephrotic syndrome. Related objectives include answers to the questions (1) does nephrosis unmask hypothyroidism and (2) does nephrosis mask hyperthyroidism?

#### METHOD

**SUBJECTS:** normals; normals treated with L-thyroxine for one month; subjects with hyperthyroidism; with hypothyroidism, primary untreated; with hypothyroidism treated for one month with L-thyroxine; with the nephrotic syndrome; subjects with the nephrotic syndrome treated for one month with L-thyroxine. All subjects will have a 24-hr urine for volume, creatinine, total protein, urine protein, electrophoresis, T<sub>4</sub>, and T<sub>3</sub>. Fasting samples will be drawn for SMAC-20, T<sub>4</sub>, T<sub>3</sub> resin, T<sub>3</sub> by RIA, TSH, THAT (an extra tube will be drawn for free T<sub>4</sub>, reverse T<sub>3</sub>, and TBG). A fasting TRH test will be done and blood for TSH will be drawn at 0, 30, and 60 mins post injection. The above procedures will be repeated after at least 30 days on one or more doses of T<sub>4</sub> for the treated groups. Urine protein electrophoresis will not be performed on urine with a total protein of <150 mg for 24 hrs; patients with known cardiovascular disease or >50 years will be excluded from the treated groups; and 24-hr urines will be obtained prior to or at least 72 hours after the TRH test.

#### PROGRESS

Two hypothyroid patients without nephrosis (studied before and after replacement therapy) and six patients with nephrosis have been studied according to the protocol. Four of the patients were studied in the untreated state only. Two patients were found to have primary hypothyroidism and were studied before and after replacement therapy. The finding of two patients with previously occult hypothyroidism suggests that nephrosis may be causing or unmasking a state of hypothyroidism. Analysis of the urine for thyroid hormones will be accomplished upon the establishment of an assay for urinary thyronines.

**STATUS:** (O)

**TITLE:** Syntex Laboratories #21-6276: Multicenter, Double-Blind, Randomized, Parallel Comparison of Two Different Dosage Regimens of Naproxen Sodium in Patients with Bone Pain Due to Metastatic Cancer

**PRINCIPAL INVESTIGATOR:** COL Friedrich H. Stutz, MC

**PROFESSIONAL ASSISTANTS:** LTC James E. Congdon, MC  
LTC Irwin B. Dabe, MC  
MAJ Thomas M. Baker, MC  
MAJ Alfred H. Chan, MC  
MAJ Howard Davidson, MC  
MAJ Timothy J. O'Rourke, MC

**WORK UNIT NO:** 83/42

#### TECHNICAL OBJECTIVE

To compare the relative efficacy and safety of a higher total daily dose of naproxen sodium (1650 mg per day for three days) to a lower total daily dose (1100 mg on day 1, followed by 825 mg on days 2 and 3) in patients with moderate to severe, persistent, bone pain due to metastatic cancer.

#### METHOD

This will be a multicenter, double-blind, randomized, parallel comparison study of 3 days duration using in-patients or suitable outpatients who will be randomly assigned to receive naproxen sodium, 1650 mg/day, for 3 days or naproxen sodium, 1100 mg on day 1 followed by 825 mg on days 2 and 3. Patients will be asked to evaluate pain severity using an analogue scale (0-99) every two hours beginning 0600 and ending at 2200 each day.

#### PROGRESS

(2/83 - 1/84) Two patients were entered at MAMC. In both patients, pain was not adequately controlled. MAMC did not accrue enough patients to meet the Syntex criteria; therefore; the protocol was terminated.

**STATUS:** (T)

TITLE: Weekly Low Dose CCNU for Extensive Adenocarcinoma of the  
Colon and Rectum

PRINCIPAL INVESTIGATOR: CPT Michael D. Stone, MC

PROFESSIONAL ASSISTANTS: COL F.H. Stutz, MC  
MAJ Thomas M. Baker, MC

WORK UNIT NO: 84/56

#### TECHNICAL OBJECTIVES

To determine the response rate of refractory adenocarcinoma of the colon or rectum to weekly low dose CCNU therapy and to determine the toxicity of weekly low dose CCNU therapy.

#### METHOD

CCNU will be administered by mouth at an initial dose of 40 mg/wk. The dose will be escalated by 10 mg after each 6 week period. Maximum dose will be 80 mg/wk. Therapy will continue until there is unequivocal evidence of tumor progression or until unacceptable toxicity occurs.

Study monitoring: CBC weekly, SMAC every three weeks, physical exam and toxicity notation every three weeks, and tumor measurement by appropriate studies every 12 weeks or more frequently at the discretion of the investigator.

#### PROGRESS

This form of therapy has been well tolerated. There has been no myelosuppression on the initial dose. However, no responses have been noted. This is not surprising because most of these patients have had previous chemotherapy. The investigators plan to accumulate at least 15 patients to confirm the lack of toxicity of this regimen.

STATUS: (O)



TITLE: Danazol Therapy for Idiopathic Thrombocytopenia (ITP)

PRINCIPAL INVESTIGATOR: CPT Michael D. Stone, MC

PROFESSIONAL ASSISTANTS: COL F.H. Stutz, MC  
LTC Irwin B. Dabe, MC  
MAJ Thomas M. Baker, MC  
MAJ Alfred H. Chan, MC  
MAJ Howard Davidson, MC  
MAJ Timothy J. O'Rourke, MC

WORK UNIT NO: 84/14

#### TECHNICAL OBJECTIVE

To determine the response of ITP patients to therapy with Danazol.

#### METHOD

Patient Eligibility: (1) All patients must meet the clinical definition of ITP to include a platelet count  $<100,000/\text{mm}^3$ , with normal or increased megakaryocytes on bone marrow aspirate and no drug use or other disease excepting SLE present known to cause thrombocytopenia. (2) Patients must be refractory to Prednisone or require unacceptably high doses to remain in clinical remission. (3) Patients may or may not have received prior splenectomy or other drug therapy. (4) All pregnant patients will be excluded.

Antiplatelet antibodies will be measured pretreatment. Danazol will be started at a dose of 200 mg QID and continued at this level for a period of 12 weeks. Antiplatelet antibodies will then be remeasured. A radioactive antiglobulin test and a radiolabelled staphylococcal protein A (SPA) will be performed on each sample. All concurrent medications will be continued at the outset of the study. If during the first 12 weeks an excellent response is obtained, concurrent medications for ITP may be decreased or at the end of the 12 weeks, the drug will be discontinued in those patients with transient or poor response. In patients with excellent, good, or fair response, the dose may be modified in an attempt to continue response at a lower drug level. Danazol may be continued indefinitely in those patients who respond with acceptable toxicity.

#### PROGRESS

Although 8-10 new ITP cases have been seen in FY 84, none has been entered in the study. This is probably due to the good responses to other forms of therapy, e.g., steroid and splenectomy. The investigators plan to try to obtain subjects for this study for at least another six months.

STATUS: (O)

TITLE: Comparison of Ticarcillin/Tobramycin vs Mezlocillin/  
Tobramycin in the Empiric Treatment of Febrile  
Granulocytopenic Patients

PRINCIPAL INVESTIGATOR: CPT Michael D. Stone, MC

PROFESSIONAL ASSISTANTS: LTC James Congdon, MC  
LTC James Higbee, MC  
MAJ Thomas Baker, MC  
MAJ Shannon Harrison, MC  
MAJ Timothy J. O'Rourke, MC  
CPT Michael W. Spangler, MC

WORK UNIT NO: 83/28

#### TECHNICAL OBJECTIVES

To assess the effect on electrolytes, with special attention to hypokalemia; assess platelet function and quantity; and assess control of infection and appropriateness of empiric antibiotic coverage.

#### METHOD

This will be a randomized, double blind study of adult, febrile, granulocytopenic patients. The study will accrue patients until 30 documented infectious episodes are included.

Entry criteria: neutropenia, defined as  $<1000$  segs plus bands; fever,  $>100.6^{\circ}\text{F}$   $39^{\circ}\text{C}$ , two values, two hours apart; not on antibiotics for one week prior to study; creatinine clearance  $>50$  ml/min or  $\leq 1.5$  mg%; and if history of Pen allergy will skin test.

Treatment: 3 mg Meziin IV q 4 hr plus 2 mg/kg Tobramycin IV loading dose, dose to be adjusted by Tobramycin levels, or 3 gm Ticar IV q 4 hr plus 2 mg/kg Tobramycin IV loading dose, dose to be adjusted by Tobramycin levels. Treat at least 3 days for evaluation, treat at least 10 days if infection is documented. No antipyretics. If cultures negative, discontinue medications when granulocytes  $>1,000$ . If cultures positive but not sensitive, off protocol and treat according to disk sensitivity. If patient has a drug reaction or is febrile longer than 7 days, off protocol.

#### PROGRESS

(11/82 - 9/84) Four patients were entered in previous years. No patients were entered in FY 84. The study had to be terminated due to an inability of the various services to coordinate the entry and laboratory portions. Also the investigators could find very few patients to meet the criteria.

STATUS: (T)

DETAIL SHEETS  
FOR  
PROTOCOLS

DEPARTMENT OF NURSING

TITLE: MAMC Department of Nursing Process Audit

PRINCIPAL INVESTIGATOR: CPT Holly Buchanan, ANC

PROFESSIONAL ASSISTANTS: LTC Mary A. Feske, ANC  
LTC Margaret Kulm, ANC  
MAJ Linda Guttman, ANC  
CPT Susan Alderson, ANC  
CPT Karl Friedl, MSC  
Rita Sorenson, DAC  
Sandy Inazu, American Red Cross Volunteer

WORK UNIT NO: 84/08

#### TECHNICAL OBJECTIVE

To assess the quality of nursing practice, identify areas that need improvement, and evaluate improvements for implementation at MAMC.

#### METHOD

A process audit study was performed by the Division of Nursing, Rush-Presbyterian St. Luke's Medical Center, and the Medicus Corporation. This process was utilized at WRAMC with computer development and support from TRIMIS Army and Ft Detrick. The original protocol included 357 criteria and is published in 3 volumes available from NTIS. For this study, 69 questions have been selected requiring four types of review: chart audit; observation; patient interview; and nurse interview. A pilot test, involving three nursing units at MAMC, will be done to establish the validity of the items selected for use. The investigators will evaluate collected data and adjust audit forms as necessary. Individuals from the Department of Nursing selected by the QA Committee will be trained in the proper conduct of the audit process and will then audit all nursing units at MAMC on a quarterly basis. Random sampling (random number table) will be used (10 patients minimum per unit). The nursing staff will be blinded to the audit. Responses to the survey will be analyzed by questions and divided by wards. The questions will be summarized into six principal categories of nursing care: plan of nursing care formulated; physical needs of patient; non-physical needs of patient; achievement of nursing care objectives evaluated; unit procedures followed for protection of patients; delivery of nursing care facilitated by administrative management. The summarized data will be evaluated by the Patient Care Evaluation Committee and used for staff development and continuing education. Subsequent audits will evaluate the effectiveness of program improvement undertaken by the unit. This study will be used by the nursing staff as part of the QA program.

#### PROGRESS

The pilot study has been completed and the process audit revised to meet the objectives of the study. Data is now being collected. MAJ Linda Guttman was the original PI on this protocol, and CPT Buchanan assumed this responsibility upon MAJ Guttman's departure.

STATUS: (O)

TITLE: Determination of Adequate Discard Volume of Blood to  
Obtain Accurate Partial Thromboplastin and Thrombin Time  
Specimens from Arterial Lines

PRINCIPAL INVESTIGATOR: MAJ Pamela K. Burns, ANC

PROFESSIONAL ASSISTANTS: MAJ Patricia M. McCormack, ANC

WORK UNIT NO: 84/45

#### TECHNICAL OBJECTIVE

To determine an adequate discard volume required to obtain accurate measurement of the partial thromboplastin and thrombin times on specimens drawn from arterial lines in critically ill patients.

#### METHOD

Thirty patients in the Intensive Care Unit with in-dwelling arterial catheters will have discard specimens of 1.1, 4.5, 5.6, and 8.3 ml drawn with 2.7 ml test specimens and flush periods in between each drawing. A stop-watch will be started before the first arterial drawing and will be stopped after the flush period after the last discard specimen is drawn. A 2.7 ml venous specimen will be obtained as a control specimen immediately before the arterial specimens are drawn.

#### PROGRESS

This protocol has not been started because the principal investigator submitted an addendum to have the volumes of the discard specimens changed and had to wait for approval from the IRB.

STATUS: (0)

TITLE: Use of a Problem Oriented Nursing Record System (PONR)  
Within an Adult Medical Nursing Setting

PRINCIPAL INVESTIGATOR: LTC Margaret M. Kulm, ANC

PROFESSIONAL ASSISTANTS: MAJ Sally Bassett, ANC  
MAJ Susan Motta, ANC  
CPT Susan Alderson, ANC

WORK UNIT NO: 84/22

#### TECHNICAL OBJECTIVE

To identify changes and/or differences produced by the introduction of an operationally defined PONR system as measured by the MAMC Process Audit which has been approved by the IRB.

#### METHOD

Components of the MAMC Process Audit correlate closely with JCAH criteria and HSC regulations related to documentation in the nursing record. Utilization of a specific operational methodology in concert with the PONR system might demonstrate an effective manner through which compliance with JCAH criteria and HSC regulations can be achieved on a consistent basis. The use of a PONR system includes documentation of the patient's progress on nursing notes (SF-510) using a format that begins with a stated problem and then lists subjective, objective information, assessment and planning (SOAP) as it relates to the stated problem; documentation of a nursing assessment (DA 3888) performed and/or reviewed by the professional nurse; development of a nursing plan of care (DA 3888-1) by the professional nurse that includes a problem list and outcome goals; use of the Therapeutic Documentation Care Plan (DA 4677) to record and confirm completion of planned nursing actions; and use of the nursing notes and nursing assessments and care plan to indicate review, resolution, and/or reevaluation of planned patient care goals.

Phase I of this study will consist of baseline collection of data prior to implementation of PONR and SOAP charting using the MAMC Process Audit; Phase II will consist of implementation of the PONR system on Wards 20 and 21; and Phase III will consist of data analysis comparing baseline data to data collected after implementation of PONR and comparing MAMC process scores from Wards 20 and 21 with like units.

#### PROGRESS

Data analysis revealed no overall statistically significant ( $>0.05$ ) component differences between the quality of care existing prior to the implementation of a PONR system and that occurring four months after implementation. However, two specific elements did show a significant difference ( $>0.05$ ): the number of times that nursing therapeutic measures occurred as part of the written plan of care and adherence to the use of the problem oriented SOAP method of charting. A repeat of the study using a content validated MAMC process audit tool on a quarterly basis with comparisons made over a greater period of time utilizing a larger sample size is recommended.

STATUS: (C)

TITLE: A Comparison of Urinary Bladder and Esophageal  
Temperature Measurement in the Anesthetized Patient

PRINCIPAL INVESTIGATOR: CPT Michael Mehlhaff, ANC

PROFESSIONAL ASSISTANTS: LTC James Temo, ANC  
CPT Philip Brown, ANC  
CPT Robert Holzman, MC  
CPT Kathleen Rice, ANC  
CPT Gary Smith, ANC

WORK UNIT NO: 84/66

#### TECHNICAL OBJECTIVE

To determine if there is a difference in the temperature recorded by esophageal temperature probes and urinary bladder temperature probes in ASA (American Society of Anesthesiologists) Category I & II female patients undergoing abdominal hysterectomy under general anesthesia.

#### METHOD

Only patients who would normally receive indwelling urinary bladder catheters will be used. The induction and maintenance of anesthesia will be by a variety of intravenous and inhalation techniques. A convenience sample of the first 20 patients who meet the proscribed criteria will be studied. Temperatures will be measured using a foley catheter with indwelling temperature sensors and esophageal temperature monitoring sensors. Both temperature probes will be attached to standard temperature monitors for direct temperature monitoring. After induction of anesthesia, the esophageal and urinary bladder probes will be placed. The first temperature measurement (to the nearest 0.1°C) will be recorded 5 minutes after the last probe has been placed, with subsequent recordings made every 15 minutes for one hour, for a total of five measurements on each subject. The data will be analyzed using the multiple paired t-test. Data reflecting temperature differences between sites will be calculated at each 15 minute interval. Level of significance will be 0.05. If the data are determined to deviate from a normal distribution, the Mann-Whitney u test will be substituted.

#### PROGRESS

Twenty patients were studied. Esophageal and urinary bladder temperatures correlated well when the bladder was not exposed to ambient temperatures. However, it was found that they did not correlate well when the bladder was exposed to ambient temperatures. The researchers believe other means of monitoring the patient's temperature should be employed in surgical procedures which expose the bladder to ambient room temperatures.

STATUS: (C)

TITLE: An Analysis of Cancelled Elective Surgical Procedures at  
MAMC

PRINCIPAL INVESTIGATOR: MAJ Jean M. Reeder, ANC

PROFESSIONAL ASSISTANTS: 1LT Jack Robson, ANC

WORK UNIT NO: 84/15

#### TECHNICAL OBJECTIVE

To determine the factors which cause scheduled elective surgical procedures to be cancelled.

#### METHOD

Data will be collected on the following categories:

##### Surgeon Caused

Overscheduled cases  
Inadequate/incomplete workup  
Lack of surgical staff  
Incorrect surgical permits

##### OR Caused

Lack of available OR time  
OR staffing problems  
Anesthesia staffing problems  
Equipment problems

##### Hospital Caused

Lack of bedspace

##### Patient Caused

Refusal  
No show  
Patient ill

##### Other

Pre-empted by emergency  
Aborted due to intra-operative complication

Determination of cancellation cause will be done jointly by the staff anesthesiologists and the operating surgeons. When more than one factor is involved in cancellation, this will be noted and prioritized. Data collection will continue daily for six months. At the end of each month, frequency distributions will be determined by surgical service and cancellation category. Cancellation rates will be determined for each service based on the total number of elective surgical cases scheduled for each month. Selected variables such as services with residency training, cancellations on certain weekdays, and specific cancellation categories may be further analyzed. Data will be compared with that from other hospitals for significant differences.

#### PROGRESS

This study was conducted at MAMC and another military medical center. Significant differences between medical centers were noted in major categories classified as OR related, patient related, and other causes. At MAMC, 40% of cancellations were patient related, 27% were surgeon related, and 21% had other causes. Some surgical cancellations are unavoidable and some are preventable.

STATUS: (C)



D E T A I L   S H E E T S  
F O R  
P R O T O C O L S

DEPARTMENT OF OB/GYN

TITLE: Mezlocillin Therapy for Empiric Treatment of Serious  
Gynecological Infections

PRINCIPAL INVESTIGATOR: COL William Benson, MC

PROFESSIONAL ASSISTANTS: LTC James Higbee, MSC  
MAJ Shannon Harrison, MC

WORK UNIT NO: 83/59

#### TECHNICAL OBJECTIVE

To compare the outcome of single drug therapy with Mezlocillin to a multiple drug regimen of ampicillin, gentamicin, and clindamycin in serious gynecological infections.

#### METHOD

Two hundred women with serious genital tract infections will be studied. Patients in which an anaerobic organism is suspected or in which patients are ill enough to indicate initial treatment with a drug directed at anaerobes will be included in the study unless they are allergic to penicillin. Patients who have been treated with an antibiotic within the past 7 days will not be entered in this study. All subject will have urine analysis and culture, CBC, SMA-20, chest x-ray, and aerobic and anaerobic cultures of blood and presumed site of infection done as appropriate. Patients will be randomly assigned to one of the two treatment groups: Group I: Mezlocillin, 300 mg/kg/day, IV, divided into 6 doses or Group II: ampicillin, 2 gms q. 4 hrs. clindamycin, 600 mgs q. 8 hrs, gentamicin, 2 mg/kg loading dose, then 1.5 mg/kg q. 8 hrs VI. Subjects will have temperatures taken at 4 hour intervals. All patients will have a CBC and ESR daily and a serum creatinine biweekly. Patients in Group II will have gentamicin levels determined at 24-36 hrs and biweekly with gentamicin dose adjusted to produce peak levels at 5-8 mcg/ml and trough levels less than 2 mcg/ml. Treatment will be continued for 5 days unless terminated earlier because of drug reaction or toxicity; pathogens resistant to the antibiotic are documented, worsening in condition requires change in antibiotic, addition of heparin, or surgery. The treatment will be considered successful if, by completion of 5 days of therapy, the patient has been afebrile for 48 hours and has a normal examination. Following successful treatment, the patient will be followed at weekly intervals for three weeks.

#### PROGRESS

In FY 84, 66 patients were entered for a total of 94 subjects. Patients continue to be entered, and no data have been analyzed.

STATUS: (O)

TITLE: Use of X-Ray Pelvimetry and Ultrasonic Parameters to  
Predict CPD and Shoulder Dystocia

PRINCIPAL INVESTIGATOR: LTC Fred H. Coleman, MC

PROFESSIONAL ASSISTANTS: COL John A. Read, MC  
LTC Edward E. Dashow, MC  
MAJ Arthur Schipul, MC

WORK UNIT NO: 84/04

#### TECHNICAL OBJECTIVE

To devise a method of predicting difficult deliveries or the need for a Cesarean section prior to labor by combining a method of measuring fetal size and maternal pelvis size.

#### METHOD

Women 37 weeks or beyond in vertex presentation, clinically felt to have a fetus over 4000 gms will be scanned on a weekly basis. An estimated fetal size will be determined from head, shoulder, abdominal, and thigh size using standard techniques. The mother will get pelvimetry done after delivery to avoid any radiation risk to the fetus, using the standard Sussman-Colcher technique or the CT scanner. Both films and ultrasound will be read by the investigators and recorded, along with the outcome and method of the delivery on 250 patients. Multiple regression analysis and least squares averaging will be used to generate an equation which will separate those women requiring Cesarean section from those in the vaginal delivery category, with a "grey zone" where shoulder dystocia may be a problem.

#### PROGRESS

(10-83/9 84) Several patients were entered on this protocol. Dr. Coleman has been reassigned to Tripler Army Medical Center where he will continue the protocol after approval from the IRB.

STATUS: Transferred

TITLE: Detection of Maternal-Fetal Hemorrhage During Exercise Throughout Pregnancy.

PRINCIPAL INVESTIGATOR: LTC Fred H. Coleman, MC

PROFESSIONAL ASSISTANTS: COL John A. Read, MC  
LTC Edward E. Dashow, MC  
MAJ Arthur H. Schipul, MC

WORK UNIT NO: 84/06

#### TECHNICAL OBJECTIVE

To test for possible maternal-fetal hemorrhage during exercises performed at various times throughout the course of pregnancy.

#### METHOD

Twenty-five volunteers active duty pregnant women and 25 non-pregnant controls involved in an exercise program will have pre and post exercise blood samples drawn. Smears will be made and processed for Kleihauer-Betke readings. Samples (10 cc) will be drawn at 16, 22, 28, 34, and 38 weeks to determine any difference in permeability throughout pregnancy. Results will then be tabulated and examined for statistical significance with standard techniques.

#### PROGRESS

(10/83 - 9/84) The investigator was unable to start the study before leaving MAMC due to the lack of initiation of the exercise program. Dr. Coleman will continue this protocol at Tripler Army Medical Center after approval by the IRB.

STATUS: Transferred

TITLE: Management of Intractable Postpartum Hemorrhage by the  
Use of 15-Methyl Prostaglandin F2 Alpha-Tromethamine Salt

PRINCIPAL INVESTIGATOR: LTC Edward E. Dashow, MC

PROFESSIONAL ASSISTANT: COL Joseph Sakakini, MC

WORK UNIT NO: 81/36

#### TECHNICAL OBJECTIVE

To study the effects of 15-methyl prostaglandin F2 Alpha-THAM given IM to individuals having postpartum hemorrhage secondary to uterine atony that have been treated with all other conventional methods.

#### METHOD

This drug will only be utilized after the conservative management has failed and the patient is then considered for a surgical procedure to stop the severe postpartum hemorrhage and only if the use of the drug is not contraindicated by asthma, hypersensitivity to the drug, active cardiac, pulmonary, renal, or hepatic disease, or a history of these conditions or anemia, jaundice, or epilepsy. At the time of infusion, the IV infusion of oxytocin will be discontinued. The IV fluids will be continued and no further methergine will be given. Vital signs will be monitored and recorded every 15 min and continued for two hours after the final injection. Hemoglobin and hematocrit will be checked at 24 and 48 hours after the last injection. The volume of blood loss after delivery and the amount of blood loss after the initial injection will be estimated and recorded. The degree of contraction of the uterus will be determined by palpation before and one-half hour after each injection. The rate of hemorrhage will be estimated one-half hour after each injection and recorded as either increased, unchanged, or stopped. The presence of lacerations of the genital tract and retained placental fragments will be ruled out prior to entrance in the study.

#### PROGRESS

(1/81 - 8/84) Eight patients have been entered. Early results were not thought to be reliable due to a possible impotent batch of medicine. In the last three patients the drug appeared to be excellent for refractory post-partum hemorrhage except with advanced uterine infection. No new patients were entered in FY 84. There were no adverse effects reported.

The drug has now been approved by the FDA.

STATUS: (C)

TITLE: Management of Premature Rupture of Membranes in Patients  
at 34-40 Weeks Gestation

PRINCIPAL INVESTIGATOR: LTC Edward E. Dashow, MC

PROFESSIONAL ASSISTANTS: COL Joseph Sakakini, MC  
MAJ Alexander R. Smythe, MC

WORK UNIT NO: 81/55

#### TECHNICAL OBJECTIVE

(1) To ascertain whether a decreased caesarean section rate will result with conservation management in the patient with rupture of membranes and an "unripe" cervix at 34-40 weeks gestation; and  
(2) to judge whether a decreased infection rate will result with conservation management in the above patient group as opposed to those where labor is medically initiated immediately in spite of the unprepared cervix.

#### METHOD

Following initial evaluation, patients who are >34 weeks gestation will be placed in three groups. Group A (Bishop's inducibility score >7) will be induced and/or augmented as expeditiously as possible and evaluated per usual obstetrical guidelines. Group B (Bishop's score <7 and odd terminal SSN digit) will be placed under observation using standard obstetrical monitoring and treated according to the progress of each patient. Group C (Bishop's score <7 and even terminal SSN digit) will be induced or augmented as soon as possible following admission to the labor and delivery unit.

#### PROGRESS

(3/81 - 9/84) A total of 62 subjects were entered. There appears to be no significant difference between waiting or immediate delivery in the 34-40 week pregnancy with rupture of membranes.

STATUS: (C)

TITLE: Comparison Study of Intrauterine Irrigation versus Intravenous Use of Mandol or Claforan During Cesarean Sections

NOTE: Title change - original title was: Comparison Study of Intrauterine Irrigation with Moxalactam Disodium, Cephapirin Sodium, Cefomandole Nafate, and Ampicillin During Cesarean Sections

PRINCIPAL INVESTIGATOR: LTC Edward E. Dashow, MC

PROFESSIONAL ASSISTANTS: COL John A. Read, M.D., MC  
LTC Fred H. Coleman, MC  
LTC Patrick Duff, M.D., MC  
LTC Carl Stones, M.D., MC  
MAJ Arthur Schipul, M.D., MC

WORK UNIT NO: 83/01

#### TECHNICAL OBJECTIVE

To compare the effects of moxalactam disodium, cephalapirin sodium, cefamandole nafate, and ampicillin in reducing febrile morbidity and the incidence of endomyometritis following cesarean section.

Addendum (Jun 84): In view of the overwhelming success of Mandol (see Progress section), the questions arose if Mandol by irrigation is as effective as IV Mandol given as a one time dose during cesarean section and, considering the results of studies by other investigators, would Claforan be more effective as a prophylactic agent than Mandol.

To answer these questions, the investigators will test patients by the same methods as the original protocol using the following groups: Group 1: 2 gm Mandol in 800 cc saline irrigation; 100 cc saline IV; Group 2: 2 gm Claforan in 800 cc saline irrigation; 100 cc saline IV; Group 3: 800 cc saline irrigation; 2 gm Mandol in 100 cc saline IV; Group 4: 800 cc saline irrigation; 2 gm Claforan in 100 cc saline IV.

#### METHOD (original protocol)

All patients undergoing cesarean section without a history of allergic reactions to cephalosporins and penicillin, without evidence of clinical chorioamnionitis, and not on antibiotic therapy will be eligible. Patients will be randomly assigned to one of five groups. All patients will receive endometrial cultures prior to irrigation and two days post-operative.

Group 1: After removal of the placenta, the uterine cavity will be cleaned manually with a wet sponge and the uterus will be delivered onto the anterior abdominal wall. A bulb syringe with 2 grams cefamandole nafate in 800 cc of saline will be used.

Comparison Study of Intrauterine Irrigation with Moxalactam  
Disodium, Cephapirin Sodium, Cefomandole Nafate, and Ampicillin  
during Cesarean Sections - Dashow

Instillation of the irrigant solution will be performed using 100 cc in the endometrial cavity. Suction of the irrigation fluid will be performed simultaneously using a standard pool tip suction apparatus. Following uterine irrigation, repair of the uterine incision will be performed in the usual manner. The area under the bladder flap will then be irrigated with 50 cc of solution after which the flap will be closed in the standard manner. The cul de sac will then be irrigated with 50 cc of solution and the uterus replaced in the abdomen. The gutters will then be irrigated by instillation of approximately 200 cc of irrigation fluid. This will then be suctioned. Debris and clots will be removed at this time. Closure of the abdominal incision will be done in the standard fashion decided upon by the operating physician. The remaining 100 cc of irrigation solution will be utilized during this time for wound irrigation.

Group 2: will receive the same treatment as Group 1; however, moxalactam will be used in a dosage of 2 gm/800 cc of saline;

Group 3: will be similar to the previous groups, except that cephapirin in a dosage of 2 gm/800 cc of saline will be used;

Group 4: 2 grams of ampicillin will be placed in 800 cc of saline and irrigated as in the other groups; and Group 5: 800 cc of normal saline will be used as an irrigant.

No additional antibiotics will be given, unless indicated for complications. A vitamin solution (Solu-B-Forte) will be added to each solution such as the identity of the solution is unknown to the operator. All patients will receive aerobic and anerobic endometrial cultures at the time of cesarean section prior to irrigation. Two days following cesarean they will again receive aerobic and anerobic cultures of the endometrial cavity. Patients will be followed at two and six weeks post-op.

Measurement of Effect - A fever index as described by ledger 14 will be utilized to measure the febrile morbidity. Oral temperatures will be recorded every four hours. The quantity of fever will be expressed in degree hours and will represent that area above the baseline of 99 degrees Fahrenheit. Post-operative course will be reviewed with regard to the sequela associated with endomyometritis, post-operative total hospital days, and cost of total antibiotic therapy during hospitalization.

#### PROGRESS

Two hundred seventy subjects were entered in the first phase of this study. Mandol decreased the post-cesarean endomyometritis rate (22% vs 3%,  $p=.01$ ) vs four other solutions.

No patients were entered in the second phase of the protocol as the investigators are awaiting approval of the addendum from HSC.

STATUS: (0)



TITLE: Beta-Thromboglobulin (BTG) Levels in the Newborn

PRINCIPAL INVESTIGATOR: CPT Virginia Hallinan, MC

PROFESSIONAL ASSISTANTS: LTC Gary Pettett, MC  
MAJ Philip V. Marinelli, MC

WORK UNIT NO: 84/44

#### TECHNICAL OBJECTIVES

To establish baseline levels of BTG in healthy, term infants at delivery; to ascertain if BTG levels remain stable or change in the immediate post-natal period; and to investigate the relationship between duration of labor and BTG levels in the newborn.

#### METHOD

Fifty healthy, appropriate for gestational age, term infants will be studied. Polycythemic infants will be excluded.

Two cc's of whole blood will be obtained from the umbilical cord at the time of delivery and by venipuncture at four hours of life. BTG determinations will be made utilizing beta thromboglobulin RIA kits. Whole blood (0.3 cc's) obtained from initial cord samples and the four-hour venipuncture samples will be placed in CBC tubes. Spun hct's and platelet counts will be obtained on these samples.

Two cc's of blood will be obtained from 10 healthy adults and BTG levels will be measured to insure reliability of the assay. Data will be analyzed to establish:: (1) average level of BTG in 25 term male infants; (2) average level of BTG in 25 term female infants; (3) intersex difference between the above groups; (4) effect of duration of labor on BTG levels; (5) effect of platelet count on BTG levels; (6) any change in BTG level over the first four hours of life.

#### PROGRESS

Twenty-four infants have been studied. Initial BTG levels in newborns delivered after active labor appear to be much higher than normal adult levels. Interestingly, the few samples obtained from patients with elective C-section have normal adult levels. Tentative plans are to also obtain samples at 72 hours to determine if a decreasing trend exists.

STATUS: (0)

ITLLE: Phototherapy for Idiopathic Hyperbilirubinemia of the  
Newborn: Comparison of Patient Response to Different  
Irradiance Doses

PRINCIPAL INVESTIGATOR: CPT Alan G. Getts, MC

PROFESSIONAL ASSISTANTS: LTC Gary Pettett, MC  
MAJ Philip V. Marinelli, MC  
CPT Angelina LePage, MC

ORK UNIT NO: 83/74

#### TECHNICAL OBJECTIVE

to compare two phototherapy regimens in the treatment of idiopathic hyperbilirubinemia of the newborn (IHN). Items to be compared are: serum bilirubin decrease during phototherapy, duration of phototherapy required to resolve IHN, and complications of phototherapy. The specific goal is to determine a preferred regimen.

#### METHOD

fifty (50) infants, >37 weeks gestation, appropriate for gestational age, who develop idiopathic hyperbilirubinemia, will be studied. Hyperbilirubinemia needing treatment will be defined as total serum bilirubin greater than 10.0 mg/dl within the first 48 hours of life or greater than 12.0 within the first 2 hours of life. Infants with other medical problems will be excluded from the study. Infants will be randomized into two treatment groups. Group I patients will receive phototherapy in dosage of 4-6 microwatts/cm<sup>2</sup>/nm at the specific wave lengths that are active. Group II patients will receive between 10 and 2 microwatts/cm<sup>2</sup>/nm. Phototherapy will be delivered using two identical Olympic Bili-Lites. Dosage delivered will be changed by varying the combinations of fluorescent bulbs in the two bili-lites. The dosage delivered will be measured using the Air Shields PR III Phototherapy Radiometer. Measurements will be made every eight hours. Laboratory data to be collected will be an initial total and direct bilirubin, hematocrit, direct Coombs' and blood type. Serial total and direct bilirubins will be drawn 4, 12, 24, 48, and 72 hours after the initiation of phototherapy. All samples will be drawn by heelstick.

#### PROGRESS

9/83 - 9/84) Thirty-seven patients were entered. Due to criteria limitations, only 13 records were acceptable and complete for recording data. Group 2 patients showed a tendency toward more rapid resolution of hyperbilirubinemia and shorter treatment requirements. There were no other significant changes between the two groups. Due to the small size of the study groups, statistical significance was not achieved. More patients could not be studied due to the transfer of Dr. Getts.

STATUS: (C)

D E T A I L   S H E E T S  
F O R  
P R O T O C O L S

DEPARTMENT OF PEDIATRICS

TITLE: Serum Haptoglobin in Ovarian Cancers

PRINCIPAL INVESTIGATOR: CPT Patsy J. Webber, MC

PROFESSIONAL ASSISTANTS: COL William L. Benson, MC  
COL Roger B. Lee, MC  
LTC Carl Stones, MC

WORK UNIT NO: 84/75

#### TECHNICAL OBJECTIVE

To determine if serum haptoglobin levels are elevated with ovarian cancer and if they decrease with tumor response to therapy in those patients found to have ovarian cancer.

#### METHOD

Sixty consecutive patients admitted for exploratory laparotomy for pelvic mass will be enrolled in the study. A pre-op serum sample (10 cc) will be drawn for haptoglobin analysis.

Those patients found to have ovarian cancer will be followed every three weeks with serum levels for as long as they are receiving treatment for the cancer and then every three months for two years while the cancer is in remission.

The serum haptoglobin concentrations will be correlated with the course of the disease and the results of the second laparotomy.

#### PROGRESS

This is a new study and no patients have been entered.

STATUS: (0)

TITLE: Maternal Unconjugated Estriol as a Predictor of Fetal Lung Maturity

PRINCIPAL INVESTIGATOR: CPT William S. Stovall, MC

PROFESSIONAL ASSISTANT: LTC Edward E. Dashow, MC

WORK UNIT NO: 83/03

#### TECHNICAL OBJECTIVE

To determine if there is a correlation between maternal levels of unconjugated estriol and fetal lung maturity as determined by L/S ratio.

#### METHOD

A maternal blood unconjugated estriol level will be obtained on all obstetrical patients who have amniocentesis for routine obstetric indications, determining fetal lung maturity by L/S measurements in patients with premature labor or prior to elective repeat cesarean sections. This will be done with approximately 30 or more patients and the data analyzed to see if there is a significant correlation between maternal estriol levels and L/S ratio.

#### PROGRESS

(10/82 - 7/84) Data on 115 cases where an indicated amniocentesis was performed and an E3 value was obtained within -3 to +1 days or with a value of  $\geq 15$  ng/ml at any time before amniocentesis were analyzed. In no case where the serum estriol value was  $\geq 15$  ng/ml was either the L/S ratio  $< 2.0$  or did RDS occur. Five cases of RDS occurred with L/S ratios of 0.5 to 2.0 and E3 values of 3.0 to 8.9 ng/ml. After 34 weeks the sensitivity of the test is only 46 and 40% for mature L/S ratios and RDS respectively, but the specificity is 100%. It is concluded that a serum unconjugated estriol value of  $\geq 15$  ng/ml appears to indicate pulmonary maturity.

A manuscript has been accepted for publication by the American Journal of Obstetrics and Gynecology.

STATUS: (C)

## Lactose Intolerance in Pregnancy: Its Identification and Treatment - Schipul

Lactose intolerance will be determined by blood assay lactose tolerance test and hydrogen breath analysis assay. Prior to the morning lactose challenge, the patient will have had an overnight fast.

After identification of a statistically significant number of controls and gravida lactose intolerant patients, and evaluation of their progeny postpartum, Part A will be completed.

### PART B

Part B will consist of the identification of additional gravida lactose intolerant patients. Lactose intolerant patients will be randomly assigned to either a treatment group or a non-treatment control group.

Therapy will consist of calcium supplementation and the use of a lactase enzyme in refrigerated milk 24 hours prior to ingestion. All prenatal clinic patients routinely have prenatal vitamins prescribed for daily use. Compliance will be stressed.

All assays given in the data base above will be performed on these patients also.

### PROGRESS

Sixty one patients have been entered who were not lactase intolerant; 110 have been entered in the lactase-intolerant non-treated group, and 51 have been entered in the treated group. Patient entry is continuing. No data has been analyzed thus far.

STATUS: (0)

TITLE: Lactose Intolerance in Pregnancy: Its Identification and Treatment

PRINCIPAL INVESTIGATOR: MAJ Arthur H. Schipul, MC

PROFESSIONAL ASSISTANTS: COL Charles Mitchell, MC  
COL John Read, MC  
LTC Edward Dashow, MC  
LTC Carl Stones, MC  
CPT Virginia Hallinan, MC  
GS/09 Rita Thompson, R.N.

WORK UNIT NO: 84/10

#### TECHNICAL OBJECTIVES

Part A - to identify lactose intolerance in gravida patients with a history of milk intolerance and/or current clinical suspicion of intrauterine growth retardation (IUGR).

Part B - to treat identified lactose intolerant gravida patients with supplemental calcium and a lactose enzyme in milk for ingestion.

#### METHOD

PART A: A dietary history and an obstetrical history including prior delivery of any infants that were small for gestational age will be obtained. Patients undergoing clinical IUGR workup will be questioned regarding possible milk intolerance. Patients with a positive history of milk intolerance but with normal gravida status will form the study group and controls will consist of female volunteers with a negative history of milk intolerance and normal gravida states. Milk-drinking habits are not to be altered.

Lab assays to include CBC, SMAC-20, Mg will be performed on fasting blood specimens of all patients and controls in the study. These same assays will be performed on the cord blood and the mother at the time of delivery. Vitamin D assay and parathyroid hormone assays would be of interest, if available. A 3<sup>rd</sup> glucose tolerance test and a calcium meal load test are planned for those patients with abnormal lactose tolerance test. Blood lactose tolerance tests and hydrogen breath assays will be performed once on all patients and controls in this study. Routine IUGR screening procedures will be performed ante-partum on all patients and controls in the study. Evaluation of infants delivered of patients and controls will consist of routine newborn parameters and Ponderal indexes, Brazelton scores, and hydrogen breath analysis will be recorded.

TITLE: The Detection of Fetal Maternal Hemorrhage in External Version and OCT via Alpha-feto-protein.

PRINCIPAL INVESTIGATOR: MAJ Arthur H. Schipul, MC

PROFESSIONAL ASSISTANTS: COL John A. Read, MC

LTC Fred H. Coleman, MC  
LTC Edward E. Dashow, MC

WORK UNIT NO: 83/12

#### TECHNICAL OBJECTIVE

To test for possible fetal-maternal bleeding during external cephalic version and oxytocin challenge testing using serum alpha-feto-protein and Kleihauer-Betke tests.

#### METHOD

Patients will be selected for oxytocin challenge testing or version by current management criteria used in the OB/GYN Department. Fifty patients reporting for versions and 100 patients reporting for oxytocin challenge testing will have pre and post blood samples drawn. The AFP levels will be determined via AFP radioimmunoassay kit and the Kleihauer-Betke via standard kit. The results will be correlated with each other and the procedures performed to determine the rate of fetal maternal bleeding.

#### PROGRESS

Approximately 30 patients were entered in the study in FY 84. Data are still being collected.

Upon the departure of LTC Coleman in July 1984, MAJ Arthur H. Schipul became the principal investigator.

STATUS: (0)



TITLE: Impact on Fetal Monitoring on the Premature Infant

PRINCIPAL INVESTIGATOR: COL David Sa'Adah, MC

PROFESSIONAL ASSISTANTS: COL Joseph Sakakini, MC  
MAJ Alexander Smythe, MC  
D. A. Luthy, M.D.  
E. B. Larson, M.D.  
K. K. Shy, M.D.  
G. VanBelle, M.D.

WORK UNIT NO: 80/48

#### TECHNICAL OBJECTIVE

To analyze the effects of electronic fetal monitoring versus traditional auscultation in infants of very low birth weight with respect to the following endpoints: (1) perinatal mortality; (2) perinatal morbidity including Apgar scores, acid-base status at birth, and frequency of intracranial hemorrhage; (3) maternal morbidity including rates of cesarean section; (4) infant neurological and psychomotor development to one year of age; (5) provider satisfaction; (6) consumer satisfaction; (7) medical decision making; and (8) cost effectiveness analysis.

#### METHOD

Follow-up will be performed on infants who have had fetal monitoring. Those fetuses which have had electronic fetal monitoring and fetal scalp blood sampling done will be followed and compared to randomized traditional auscultation fetal heart rate. Comparisons of fetal outcome and well-being will be made. A comparison will be made of infants <1100 gm and >1100 gm. Infants will be followed and evaluated for evidence of retardation, cerebral palsy, and hearing loss at 6 months, 1 year, 1 1/2 years, and 2 years.

#### PROGRESS

Subject entry has been completed at MAMC. Newborns entered in the study are still in follow-up at the University of Washington. Analysis of data will begin when collection of data has been completed, probably 1985. Accumulation of cases has taken twice as long as originally planned (two years).

STATUS: (O)

TITLE: Diamine Oxidase Levels and Asthma in Pregnancy

PRINCIPAL INVESTIGATOR: CPT Gloria A. Richard-Davis, MC

PROFESSIONAL ASSISTANTS: MAJ James S. Little, MSC  
MAJ Rebecca Sullivan, MC  
CPT Julie Ducey, MC  
CPT Diane J. Madlon-Kay, MC

WORK UNIT NO: 81/73

#### TECHNICAL OBJECTIVE

To determine if a correlation exists between serum diamine oxidase levels and disease activity in pregnant asthmatic women.

#### METHOD

Approximately 25 new obstetric patients who have had an asthma attack within the previous three years and a control group of 12 newly pregnant non-asthmatic women will have a detailed history taken. In particular, any history of allergy, hayfever, or smoking will be noted, and in asthmatics the frequency and severity of attacks and their treatment. In addition to the routine initial laboratory tests, the patients will have determinations of their diamine oxidase levels and spirometry measurements of FVC AND FEV. At every clinic visit, the asthmatic patients will be examined for wheezing and questioned in particular about their respiratory symptoms and medications. Every four weeks and at six weeks postpartum both the control and asthmatic patients will have spirometry and diamine oxidase determinations. The asthmatic patients' clinical conditions during pregnancy will be classified as worse, unchanged, or improved by evaluating the change in respiratory symptoms, severity of wheezing on physical exam, medication changes required, and spirometry. A chi-square analysis will be done to determine if any correlation exists between the diamine oxidase levels and the asthmatic patients' clinical conditions.

#### PROGRESS

Upon the departure of CPT Ducey in June 84, CPT Richard-Davis assumed the role of principal investigator.

Enrollment of pregnant patients is complete and data are now being collected on additional controls.

STATUS: (O)

TITLE: Clinical Evaluation of a Continuous Tissue pH Monitor for Intrapartum Fetal Monitoring

PRINCIPAL INVESTIGATOR: COL John A. Read, MC

PROFESSIONAL ASSISTANTS: MAJ Jerone N. Kopelman, MC  
MAJ Arthur H. Schipul, MC

WORK UNIT NO: 84/68

#### TECHNICAL OBJECTIVES

To ascertain the clinical accuracy during labor of continuous tissue pH with simultaneous measurement of fetal scalp and umbilical arterial pH samples; in particular to document pH and its changes in postdates patients with thick meconium; document factors which might cause discrepancies between methods; ascertain practicality and reliability of fetal tpH monitoring system and skill level required for use; determine *in vivo* drift of system in clinical use; determine incidence and type of maternal and fetal complications due to tpH probe.

#### METHOD

The probe will be used in conjunction with standard fetal monitoring. Probe will be applied only to patients where pH measurements are clinically indicated in term or post-date fetuses with vertex presentations and cervical dilation of at least 6 cm and descent to station 0 or below. The cervix should not be posterior. The clinical appearance and the palpated turgor of the fetal scalp will be recorded and the probe prepared and attached per instructions in the manual. Difficulties in application, bleeding, or obtaining data will be noted, along with problems of mother or fetus caused by application. Intrapartum fetal scalp capillary pH measures will be obtained while monitoring the tpH and compared to the tpH value. Fetal scalp capillary pH will be obtained during Stage II of labor for comparison with the simultaneous intrapartum tpH values. Umbilical arterial blood pH will be obtained at delivery for comparison with last intrapartum tpH or simultaneous tpH post-partum. Maternal venous pH will be measured during monitoring as a check on both the tpH and the capillary pH and as an indication of the cause of fetal pH changes. Corometrics pH system will be used in addition to laboratory determinations.

#### PROGRESS

The equipment has been set up and is functioning. No suitable patients have been found for the study.

STATUS: (0)

TITLE: Effects of Position on the Second Stage of Labor and Delivery

PRINCIPAL INVESTIGATOR: COL John A Read, MC

PROFESSIONAL ASSISTANTS: LTC Fred H. Coleman, MC  
LTC Edward E. Dashow, MC  
MAJ Arthur H. Schipul, MC  
CPT Virginia Hallinan, MC

WORK UNIT NO: 84/05

#### TECHNICAL OBJECTIVE

To examine and correlate the effects of various positions, such as sitting, lying, and lateral Sims, on the length of the second stage of labor, the strength and frequency of contractions, the patient's comfort, and the fetal heartbeat.

#### METHOD

A group of 75 patients, pregnant for the first time, will be randomly assigned to one of three groups - a supine group, a lateral Sims group, or an upright group. Patients will be uncomplicated, at term (between 37 and 42 weeks), and have had a normal first stage. Internal monitoring of uterine activity and fetal heart condition will be done on a continuous basis throughout the second stage. All tracings will be examined for frequency, duration, and amplitude of contractions, uterine activity and Montevideo units, fetal distress, length of second stage, patient comfort, and the development of complications of delivery. No anesthesia other than local will be used. The results will be compared using Student's t test, chi square, or Mann-Whitney U test as required by the various types of data collected.

#### PROGRESS

This protocol was originated by LTC Coleman. Upon his departure from MAMC in July 1984, COL John Read became the principal investigator. No patients have been entered at this point, but the investigators will begin to enter patients within a few months.

STATUS: (O)

TITLE: Randomized Trial of Ambulation vs Oxytocin for Labor Enhancement

PRINCIPAL INVESTIGATOR: COL John A. Read, MC

PROFESSIONAL ASSISTANTS: LTC Edward E. Dashow, MC  
LTC Frederick H. Coleman, MC

WORK UNIT NO: 83/02

#### TECHNICAL OBJECTIVE

To compare the efficacy of ambulation vs oxytocin in cases of dysfunctional labor or so called dystocia.

#### METHOD

Patients who have failed to progress in labor for one hour, >4 cm dilated, and requiring augmentation of labor are eligible. Membranes shall have been ruptured and direct internal fetal monitoring in use, showing no evidence of fetal distress. Patients should not have received analgesia or sedations for at least one hour and should not be drowsy or exhausted. Patients will be placed on the fetal monitor in the right or left lateral decubitus position. There will be a 30 minute observation period during which time uterine activity will be quantified: uterine activity units on line, Montevideo units; contraction frequency; intensity and baseline tonus; fetal heart rate pattern and variability; and progress in effacement, dilation, and station.

Group I: Using either a cable or 2-channel telemetry the patient will assume the vertical position. Exams will be conducted at one and two hours, noting the parameters stated above. If after 2 hours no progress has occurred, the patient will be returned to bed and oxytocin utilized. If good progress is being accomplished, the patient may continue ambulation if she chooses.

Group II: Continuous IV infusion of oxytocin will begin at 0.5 mu/min and increased every 15 min until contractions are every 2 1/2-3 min and >50 mmHg in intensity. Patient will be in the right or left lateral decubitus position and the parameters noted above will be measured. If at the end of two hours there is no progress and other conditions are met, the patient will be given the option to ambulate.

Length of labor, time from study entry to delivery, type delivery, 1 and 5 min Apgar scores, cord blood gasses, maternal pain perception, newborn weight and neonatal problems will also be noted.

#### PROGRESS

No patients have been entered. The investigators hope to activate this protocol within a few months.

STATUS: (O)

TITLE: External Cephalic Version with Tocolysis Using Ritodrine

PRINCIPAL INVESTIGATOR: MAJ David J. Magelssen, MC

PROFESSIONAL ASSISTANTS: COL John A. Read, MC  
LTC Edward E. Dashow, MC  
MAJ Arthur H. Schipul, MC

WORK UNIT NO: 83/17

#### TECHNICAL OBJECTIVE

To determine if the incidence of breech birth can be decreased by external cephalic version using Ritodrine to relax the uterus.

#### METHOD

One hundred gravidas with breech presentation >36 wks weeks gestation will be studied. Ultrasonography will be performed to confirm the breech presentation; measure biparietal fetal diameter to assess gestational age; quantify amount of amniotic fluid; rule out fetal cephalic anomalies and/or hyperextension; localize placenta. If the mother is Rh negative, a Kleihauer-Betke test on blood samples will be done pre and post procedure. Rhogam will be administered if indicated. A pre and post procedure fetal activity determination test will be done by external fetal monitoring. At this point the subjects will be randomized to a treatment group and a control group. The treatment group will be administered Ritodrine by IV infusion at 200 µg/min for 20 min. External cephalic version will then be attempted and a successful procedure will be confirmed by ultrasonography. The treatment group will go straight to the external cephalic version. Any patients with evidence of a compromised fetus with a nonreactive fetal activity determination test; congenital anomalies by ultrasonography; oligohydramnios; or placenta previa will be excluded.

#### PROGRESS

Approximately 18 patients have been entered in the study. Preliminary data are inconclusive but clinical observations appear to indicate that ritodrine is not effective in aiding external cephalic version if the version attempt has failed without the use of tocolysis. The protocol will be continued until adequate subject numbers are reached to attain reliable results.

STATUS: (0)

TITLE: Effectiveness of Penicillin Treatment for the Symptoms  
of Streptococcal Pharyngitis

PRINCIPAL INVESTIGATOR: LTC Marvin S. Krober, MC

PROFESSIONAL ASSISTANTS: LTC James W. Higbee, MSC

WORK UNIT NO: 84/13

#### TECHNICAL OBJECTIVE

To determine if early penicillin treatment of streptococcal pharyngitis alters the clinical course of the illness.

#### METHOD

Pediatric patients, who meet the criteria, with a complaint of sore throat or with pharyngeal inflammation on physical exam will be evaluated for the likelihood of streptococcal infection by the scoring system of Breese. Additional symptoms will be recorded to see if added data can improve our accuracy in predicting streptococcal infection, as demonstrated by throat culture. On the first visit patients will be randomly assigned to receive penicillin V, 250 mg, three times daily for three days, or placebo, have a throat culture, and a blood sample drawn for strep antibodies (active). At 24 hours subjects will have a physical exam with symptoms recorded and a throat culture. At 48 hours, subjects will have a physical exam with symptoms recorded, a throat culture, and a urine analysis for compliance with taking the prescribed medication. At 72 hours subjects will have a physical exam with symptoms recorded, a throat culture, and the treatment code will be broken and penicillin provided as necessary. Ten days will be the end of treatment and a throat culture will be obtained if the original was negative. At 3-4 weeks, another throat culture will be obtained and a blood sample taken for strep antibodies (convalescent). Patients unable to return at 72 hours will be retained in the study, but those who fail to return at 24 or 48 hours will be dropped from the study. Patients unable to return at 72 hours will have throat culture results obtained and penicillin treatment given as needed at the 48-hour visit.

This protocol has had prior approval by the IRB at TAMC. Twenty-two patients have completed the study there (14 on placebo and 8 on penicillin). An additional 25 patients are needed for the results to attain appropriate statistical significance. Data collected at TAMC will be compiled with the data collected at MAMC for further analysis.

#### PROGRESS

(11/83 - 9/84) Five patients were entered at MAMC. Symptoms resolved more quickly for those children treated with penicillin. Only the patients receiving penicillin demonstrated significant symptomatic improvement in 24 hours. Differences in symptomatology were less marked at 48 hours and almost all patients felt well by 72 hours regardless of the treatment given.

STATUS: (C)

TITLE: Mechanical Ventilation of Newborn Premature Lambs: The Effect of Frequency, I:E Ratio, PIP, and PEEP on Oxygenation and Ventilation

PRINCIPAL INVESTIGATOR: MAJ Philip V. Marinelli, MC

PROFESSIONAL ASSISTANTS: LTC Gary Pettett, MC  
MAJ Stanley P. Liebenberg, VC  
CPT Richard Meidell, MC

WORK UNIT NO: 82/26

#### TECHNICAL OBJECTIVE

To prospectively evaluate the effect of ventilator setting, specifically frequency, I:E ratio, PIP, and PEEP, on arterial oxygenation and minute ventilation in premature newborn lambs.

#### METHOD

Premature or term lambs (125-135 days gestation) will be delivered via C-section, intubated with cuffed endotracheal tubes, paralyzed with Pavulon, and ventilated with the Sechrist ventilator. All animals will have prophylactic chest tubes inserted bilaterally to prevent symptomatic pneumothoraces during the experiment. Catheters will be placed in the descending aorta through femoral artery cutdowns. The aortic blood pressure will be maintained at 50-70 mm of mercury by infusions of maternal blood and/or lactated Ringer's solution. Initially, ventilator settings will be a rate of 30, inspiratory time of 1 sec, expiratory time of 1 sec, and sufficient PIP and PEEP to deliver an adequate tidal volume while maintaining a normal  $P_{aO_2}$  and  $P_{aCO_2}$ . The sequential changes in rate will be made, maintaining the baseline PIP and PEEP. At the completion of each change, the fetus will be returned to baseline until values are stabilized before proceeding to the next step. Subsequent changes in I:E ratio, maintaining a constant rate PIP and PEEP, will be studied. The fetus will be returned to baseline settings between each step. Third, changes in PIP will be employed with a constant rate, constant I:E ratio, and a constant PEEP. Finally, changes in PEEP will be determined by maintaining a constant rate, a constant I:E ratio, and a fixed peak inspiratory pressure. Arterial blood gases will be determined prior to and immediately following each portion of the experiment. Lung tissue will be obtained from each lamb for microscopic examination.

#### PROGRESS

(2/83 - 8/84) This study was terminated because time mated lambs could not be obtained before the departure of the principal investigator. In previous years, four sets of twins were lost secondary to maternal anesthesia. Five term sheep were utilized; no premature sheep were used because of mating-time schedule difficulties. Only rudimentary data were collected.

STATUS: (T)



TITLE: Mean Airway Pressure: Significance During Mechanical Ventilation in Neonates

PRINCIPAL INVESTIGATOR: MAJ Philip V. Marinelli, MC

PROFESSIONAL ASSISTANTS: LTC Gary Pettett, MC  
CPT Richard Meidell, MC

WORK UNIT NO: 82/27

#### TECHNICAL OBJECTIVE

The specific aspects of the respiratory cycle during mechanical ventilation which allow optimal gas exchange are controversial. Recently, the concept of mean airway pressure as a composite of all pressures has been employed. It has been shown that mean airway pressure correlates directly with oxygenation. The purpose of this study is to examine the effect of various ventilator settings on gas exchange while maintaining a constant mean airway pressure.

#### METHOD

All neonates requiring intermittent mandatory ventilation will be eligible for the study. Indications for mechanical ventilation will be based on the standard criteria ( $P_aCO_2 > 60$  Torr,  $pH < 7.25$  and/or  $aPO_2 < 50$  Torr,  $F_iO_2 > 0.6$ ). A pressure limited time-cycled ventilator will be used. PIP, PEEP, inspiratory time, flow rate, ventilator rate, and  $F_iO_2$  will be adjusted to provide a  $P_aO_2$  of 50-80 Torr and a  $P_aCO_2 < 60$  Torr,  $pH$  of 7.30-7.40. The initial combination of settings producing these values will be taken as the baseline ventilator settings. Mean airway pressure will be measured from the T piece of the ventilator circuit using a proximal airway ventilator monitoring system which provides a constant digital display of the mean airway pressure by sampling proximal airway pressures every 10 mmsec and averaging these values over time. After achieving a steady state on baseline ventilator settings, an arterial blood sample will be obtained and the following sequential changes will be made on the ventilator:

Experiment I: PIP increased by 20% of baseline value and duration of positive pressure (inspiratory time) will be decreased in order to achieve the same baseline mean airway pressure. The other ventilator settings will be maintained at baseline value. All settings will then be returned to the initial baseline values.

Experiment II: PIP will be decreased by 20% of baseline value and inspiratory time will be increased to maintain a constant mean airway pressure; the other ventilator settings will be held constant.

Mean Airway Pressure: Significance During Mechanical Ventilation  
in Neonates - Marinelli

Following a 10 min equilibration period, arterial blood gas will be sampled. Vital signs will be continuously monitored. In addition, a transcutaneous  $PO_2$  monitor will be used to insure that no detrimental increase or decrease in  $P_{aO_2}$  occurs as the result of experimental changes. This sequence will be followed in the first 24 hours of the infant's life and repeated during the second and third day in order to observe whether the natural change in compliance of the lungs will change the significance of mean airway pressure.

Each of the infants will serve as its own control. Statistical analysis of pH and  $P_{aO_2}$  and  $P_{aCO_2}$  will be performed utilizing Student's t test for paired data. The  $\Delta PO_2$  gradient will be calculated from each of the blood gas results in order to standardize  $P_{aO_2}$  values over a range of  $F_iO_2$  concentrations. These ratios will be analyzed by the means of the t test for paired data.

PROGRESS

(2/82 - 8/84) Data were collected on 15 infants with no adverse effects. Data analysis is in progress.

STATUS: (C)

TITLE: Modified Immune Serum Globulin in Neonates

PRINCIPAL INVESTIGATOR: MAJ Philip V. Marinelli, MC

PROFESSIONAL ASSISTANTS: LTC G. Fischer, MC  
LTC Gary Pettett, MC  
LTC J. Pierce, MC  
MAJ Robert M. Skarin, MC  
CPT Richard Meidell, MC

WORK UNIT NO: 82/28

#### TECHNICAL OBJECTIVE

To evaluate Modified Immune Serum Globulin (MISG) as an adjunct to antimicrobial therapy in the treatment of neonatal Group B streptococci (GBS) disease. This protocol will analyze the ability of MISG to elevate neonatal IgG levels and will specifically look at pre and post MISG sera for evidence of increased activity against Group B streptococci using *in vitro* assays for opsonic antibody.

#### METHOD

Human MISG will be screened to ensure activity against several strains of GBS and one lot of 5% MISG will be selected and used throughout the study. Neonates who have a clinical diagnosis of suspected or proven sepsis will be evaluated and treated in the standard fashion and will also receive MISG. Infants thought to be in need of blood products will be excluded from the study. All infants will have cultures for bacterial pathogens taken prior to antibiotic or MISG therapy which will include umbilical, gastric aspirate, urine, blood, and cerebral spinal fluid. A 2.0 ml blood sample (prespecimen) will be obtained just prior to starting antibiotics and MISG therapy. A second 2.0 ml specimen will be obtained 2 hours after the completion of MISG infusion and again at 1, 2, 3, and 6 weeks after the infusion. The material will be given as 5% human MISG in a 10% maltose solution. The dose will be 250 mg/kg or 5 ml/kg to be given as a 30 minute infusion. Standard supportive care will be given to all other neonates treated for proven or suspected sepsis. All patients receiving MISG will be required to have constant temperature, heart rate, and respiratory monitoring. Patients with an umbilical artery catheter will have continuous BP monitoring. If not, BP by the Doppler method will be obtained before infusion, every 15 minutes after infusion for at least 2 hours, and then every hour for at least 24 hours. Urine volume, protein, and reducing substances will be measured at each void for the first 24 hours after MISG administration. Serum sodium, potassium, BUN, chloride, calcium, glucose, and osmolality along with hematocrit, hemoglobin, platelets and white blood cell count with differential will be

## Modified Immune Serum Globulin in Neonates - Marinelli

obtained before, 2 hours after, and twice weekly for 2 weeks following the infusion. After the blood specimen is obtained, the serum will be separated and stored at -70°C. Immunoglobulin levels will be determined by standard immunodiffusion assay and opsonic antibody to GBS will be measured using the bactericidal opsonophagocytic assay currently used in the MAMC lab. In addition, a chemiluminescent assay, which measures activation of the hexose-monophosphate shunt, is being developed and will be utilized to measure functional antibody to GBS. All patients will be followed for a minimum of 6 weeks. The infants will be evaluated for growth and development and will receive all standard immunizations and care.

### PROGRESS

(2/82 - 8/84) Data was collected on four patients at MAMC and forwarded to WRAMC for analysis.

The results of this protocol are currently being analyzed in preparation for a final publication. As the project was a multicenter study, the data from the entire project is not completely available. Preliminary results suggest that, as given in this protocol, intravenous immune serum globulin is a safe drug with a predictable pharmacokinetic pattern.

Further investigation in this area will continue under the protocol entitled "Prophylactic Intravenous Immunoglobulin in High Risk Neonates" (MAMC #84/73) with MAJ Bruce Willham, MC, as the principal investigator at MAMC.

PUBLICATION: Weisman, L, Fischer, G, Marinelli, P: Intravenous Immunoglobulin Therapy in the Neonate. A Study of Pharmacokinetics and Safety. Pediatric Research 17(4): 341, 1983.

Fisher, GW, Weisman, LE, Hemming, VG, et al: Intravenous Immunoglobulin in Neonatal Group B Streptococcal Disease. Pharmacokinetics and Safety Study in Monkeys and Humans. Amer J Med 76:117, 1984.

PRESENTATION: A paper was presented at the American Academy of Pediatrics, New York, New York, Oct 83

STATUS: (C)

TITLE: Hydrogen Breath Analysis After First Feedings in Infants  
in Intensive Care Nursery

PRINCIPAL INVESTIGATOR: COL Charles Mitchell, MC

PROFESSIONAL ASSISTANTS: MAJ James Little, MSC  
CPT Richard Meidell, MC

WORK UNIT NO: 81/107

#### TECHNICAL OBJECTIVE

To determine if there is malabsorption in infants in the intensive care nursery after first feedings and if there is predictive value of impending necrotizing enterocolitis in those infants who have malabsorption.

#### METHOD

A minimum of 20 patients will be studied before and after one of the initial feedings of formula. Expired air will be obtained at 0, 2, and 4 hours. In infants mechanically ventilated, the air may be obtained via a one-way volume. Non-ventilated infants will have sampling obtained from a catheter nasal apparatus connected to a syringe. Breath hydrogen will be measured by gas chromatograph equipped with a reduction gas detector.

#### PROGRESS

(8/81 - 9/84) This protocol had to be terminated, primarily due to problems with the equipment. No patients were entered.

STATUS: (T)

TITLE: Hydrogen Breath Analysis in Normal Newborns

PRINCIPAL INVESTIGATOR: COL Charles Mitchell, MC

PROFESSIONAL ASSISTANTS: MAJ James S. Little, MSC  
CPT Richard Meidell, MC

WORK UNIT NO: 81/108

#### TECHNICAL OBJECTIVE

To determine if normal newborns malabsorb any of their formula feedings.

#### METHOD

A minimum of 30 patients will have samples taken of expired air. This will be done using a painless catheter apparatus in one anterior nares. The samples will be taken before the first feeding, at 2 hours and 4 hours. Breath hydrogen will be measured by gas chromatograph equipped with a reduction gas detector.

#### PROGRESS

(8/81 - 9/84) This protocol had to be terminated, primarily due to problems with equipment. No infants have been entered on the protocol.

STATUS: (T)

TITLE: Hydrogen Breath Analysis in Children with Chronic  
Nonspecific Diarrhea

PRINCIPAL INVESTIGATOR: COL Charles Mitchell, MC

PROFESSIONAL ASSISTANTS: MAJ James S. Little, MSC  
MAJ Marsha Van Wagner, ANC

WORK UNIT NO: 81/109

#### TECHNICAL OBJECTIVE

To determine if ingestion of various carbohydrates is related to the chronic non-specific diarrhea syndrome; the hypothesis being that malabsorbed carbohydrates act osmotically to increase the fluid content of stools and that malabsorbed molecules are fermented by clonic bacteria producing hydrogen; therefore, hydrogen detected in the breath of previously fasting patients implicates malabsorption and subsequent diarrhea.

#### METHOD

Subject will be tested, fasting, on three different mornings. First test - cereal given without milk, using water as the fluid; second test - lactose as 20% solution; third test - sucrose. After the feeding the breath will be sampled at 0, 60, and 120 minutes. The breath will be sampled by a large catheter inserted into the anterior nares, a finger pressed against the opposite nares. A smaller tube will be inserted into the larger and attached to a syringe. At midexpiration, a few ml will be aspirated to a total of approximately 20 ml and insufflated into a vacuum test tube. Breath hydrogen will be measured by gas chromatograph equipped with a reduction gas detector.

#### PROGRESS

(8/81 - 9/84) This protocol had to be terminated, primarily due to problems with equipment. No infants have been entered on the protocol.

STATUS: (T)

TITLE: Somatomedin-C and Gonadal Hormones in Precocious Sexual Development and in Relation to Medroxyprogesterone Treatment

PRINCIPAL INVESTIGATOR: LTC Dan C. Moore, MC

PROFESSIONAL ASSISTANTS: COL Stephen R. Plymate, MC  
Vincent C. Kelley, M.D.

WORK UNIT NO: 81/113

#### TECHNICAL OBJECTIVE

To define the abnormalities of pituitary, adrenal, and gonadal function in patients with precocious sexual development in order to discern whether certain laboratory determinations correlate with clinical stages of sexual precocity and can be predictive of subsequent course; to discern whether any of these same parameters can be used to predict response to medroxyprogesterone therapy; and to assess the relative effect of medroxyprogesterone in suppressing somatomedin-C and sex steroids of gonadal vs adrenal origin.

#### METHOD

Thirty patients with precocious sexual development (males under 9 years and females under 8 years) will be given a physical examination rating of puberty status according to the system of Tanner. Plasma LH, FSH, E<sub>1</sub>, E<sub>2</sub>, T, DHEAS, bone age films, and skull films will be done. Blood samples will be drawn for somatomedin-C, somatomedin bioassay,  $\Delta$ 4-androstenedione and SHBG. Once a diagnosis is made, patients will be followed at 3 month intervals according to standard procedure. Those patients in whom it is clinically indicated will be placed on medroxyprogesterone therapy (100-200 mg IM every 2 weeks). Those patients placed on medroxyprogesterone will have initial blood tests repeated at 3 and 6 months to assess effect of therapy.

#### PROGRESS

(8/81 - 1/84) Thirty three subjects were entered in previous years. No additional subjects were entered in FY 84. This study had to be terminated because the coinvestigator from the University of Washington, who was to do part of the determinations, left the university and the PI was unable to get someone to replace him.

STATUS: (T)



TITLE: Eating Attitude Questionnaire

PRINCIPAL INVESTIGATOR: LTC Dan C. Moore, MC

PROFESSIONAL ASSISTANTS: None

WORK UNIT NO: 84/77

#### TECHNICAL OBJECTIVE

To determine the prevalence among an unselected population of military adolescents of dissatisfaction with body weight or appearance, of efforts to alter weight, and of methods used.

#### METHOD

Questionnaires will be given to 1,000 consecutive adolescent patients (male and female). Those self-identified as having a problem with eating who request help will be appropriately evaluated and counselled. Questionnaires will be analyzed to develop a statistical profile of eating behaviors in the population studied. If warranted by the data, an ongoing program may be developed to identify and treat patients with eating problems. Data will be organized descriptively and subsequently analyzed using analysis of variance.

#### PROGRESS

Three hundred and fifty-four (354) subjects have been entered. The investigator is still in the process of collecting data.

STATUS: (0)

TITLE: A Teaching Model for Pediatric Intubation Utilizing  
Ketamine-Sedated Kittens

PRINCIPAL INVESTIGATOR: LTC Gary Pettett, MC

PROFESSIONAL ASSISTANTS: COL Errol R. Alden, MC  
COL Paul B. Jennings, VC  
LTC Ronald W. Brenz, MC

WORK UNIT NO: 74/19

#### TECHNICAL OBJECTIVE

To teach infant resuscitation procedures to nurses, nurse clinicians, OB-GYN residents, and other nonpediatric physicians who may be called upon to treat pediatric emergencies. Many physicians and paramedics have never had the training opportunity to attempt intubation of an awake living creature. The kitten, immobilized with ketamine hydrochloride, gives the student the opportunity to visualize vocal cords, precipitate laryngospasm, and learn the difficulties associated with emergency intubation.

#### METHOD

Weaned kittens, weighing 0.5 to 1.0 kg will be used in these teaching sessions. Ketamine hydrochloride (22 mg/kg) plus atropine sulfate (0.04 mg/kg) will be administered intramuscularly to each kitten. Intubation will be performed with the kittens on their backs, using a pediatric laryngoscope, and sizes 8-14 French endotracheal tubes. Kittens may be used for several consecutive weekly sessions until they grow too large to be utilized. The procedure is not harmful to the kittens.

#### PROGRESS

This course was given on one occasion during FY 84. The protocol has been temporarily suspended by order from DA.

There has been a publication that was well received from this protocol and an exhibit has been presented at four scientific meetings. It won the Gold Award for Outstanding Exhibit for Teaching Value at the Annual Meeting of the American Academy of Pediatrics, 1976.

STATUS: Suspended

ITLE: Techniques of Advanced Life Support

RINCIPAL INVESTIGATOR: LTC Philip G. Pettett, MC

ROFESSIONAL ASSISTANTS: COL Barry Wolcott, MC  
LTC Stan Harris, MC  
LTC William A. Madden, MC  
MAJ Steve Dronen, MC  
MAJ Philip V. Marinelli, MC  
MAJ Stanley P. Liebenberg, VC

ORK UNIT NO: 83/35

#### TECHNICAL OBJECTIVE

o provide experience for physicians/nurse personnel in the echniques of advanced life support. This program will provide he student with familiarity in the skills of thoracotomy, ercutaneous/venous puncture, arterial venous cutdown, vascular ine insertion and tracheostomy placement.

#### METHOD

he animal models will be mongrel dogs. Each animal will be roperly prepared for standard surgical techniques by shaving nd scrubbing. Surgical procedures will be performed in a sterile anner with the animal fully anesthetized and supported by proper entilatory technique. Each animal will then undergo the following urgical procedures using techniques currently in hospital practice or humans:

- (1) thoracotomy with pleural tube insertion
- (2) percutaneous arterial and venous cannulation with IV lines
- (3) arterial and venous cutdown with IV line insertion
- (4) tracheostomy insertion

t the conclusion of the experiment, surgical sites will be roperly closed and the animal given a lethal dose of barbiturate ithout being allowed to regain consciousness.

#### PROGRESS

his is a teaching protocol and is given to all Pediatric esidents on an annual basis. There was one session early n the year. The protocol has been temporarily suspended by rder from DA.

TATUS: Suspended

TITLE: Changes in Reading Performance of Children with Reading Delays and Optometric Binocular Dysfunction When Treated with Vision Therapy, Prospective Investigation

PRINCIPAL INVESTIGATOR: COL Carl A. Plonsky, MC

PROFESSIONAL ASSISTANTS: CPT Quentin A. Humberd, MC  
CPT John B. Van Ginhoven, MSC

WORK UNIT NO: 84/81

#### TECHNICAL OBJECTIVE

To test the hypothesis that vision training in children with reading delays and optometric binocular dysfunction can improve reading performance more than standard treatment over a five-month study period, using a standardized educational test to measure change in reading performance.

#### METHOD

Subjects will be selected from eligible military dependent children with known delays in reading who are enrolled in special remedial reading classes. A standardized educational test of reading performance will be administered by a qualified educational psychometrician to determine the child's baseline reading performance and severity of reading delay. All educators and evaluators will be blinded to any subsequent treatment group assignment during the study period. The children will then be evaluated for binocular dysfunction, and those children found to have optometric binocular dysfunction will be entered in the study. No child will be accepted if he has ever received optometric or vision therapy in the past. The general learning abilities will be in the normal or average range with a fairly specific problem in the area of reading. No student will be accepted who has more extensive neurodevelopmental delays or behavior problems requiring medication. Participants will be stratified by severity of reading delay, age, and severity of diagnosed binocular dysfunction. In addition, each stratum will be blocked in groups of 6 so that the investigator will randomly assign treatment groups from equal numbers of participants in each stratum. Group A will receive individualized vision therapy for a 5-month period. Group B will be receive individualized remedial instruction at the Pediatric Clinic and with the parents for 5 days each week. This group's activities will be designed to parallel Group A in terms of the time used for intervention. Group C will continue to receive only the same educationally based remedial reading for a 5-month period. At the completion of the 5-month study period, all subjects will be retested to determine change in reading delay.

#### PROGRESS

This is a new protocol which has not been started to date.

STATUS: (0)

TITLE: Effects of Common Arthroscopic Irrigating Solutions  
and Marcaine on Adult Rabbit Articular Cartilage:  
An *In Vivo* Study

PRINCIPAL INVESTIGATOR: CPT Robert A. Arciero, MC

PROFESSIONAL ASSISTANTS: LTC Thomas Parr, MC  
MAJ Stanley P. Liebenberg, VC  
MAJ James S. Little, MSC

WORK UNIT NO: 84/50

#### TECHNICAL OBJECTIVE

To assess the effects of commonly used arthroscopic irrigating solutions and Marcaine on articular cartilage proteoglycan synthesis. In this case it will be possible to determine if these commonly used agents, which are required for arthroscopic knee surgery, have any deleterious effects on articular cartilage synthesis.

#### METHOD

Three groups of 18 adult New Zealand white rabbits weighing 1.5 - 3.0 kg will be anesthetized with Ketamine (25 mg/kg) and Rompum (1.1 mg/kg) and maintained in a state of anesthesia with halothane (0.5%). The right knee capsule will be exposed by surgical dissection. Continuous inflow and outflow irrigation will be established for two hours using normal saline, Ringer's lactate, or sterile water. At the completion of irrigation, 100  $\mu$ Ci of  $^{35}\text{SO}_4$  in 0.3 ml saline will be injected into the knee. At three different times (as determined in pilot studies, probably 30, 60, and 90 min) the rabbits will be killed and the cartilage from the right knee will be excised. The cartilage from the left knee (this knee has not been irrigated or injected with radioactivity) will also be excised. The samples will be blotted, weighed, and washed 3 times in distilled water (20 ml/0.2 gm cartilage) to remove unincorporated radioactivity. Samples will be counted in Aquasol in a liquid scintillation spectrometer. Counts/minute/gm cartilage will be plotted against incorporation time. Results will be compared using the unpaired Student's t test. If preliminary results determine that no radioactivity is incorporated in the left knee (knee which is not injected with isotope) then subsequent experiments will use both right and left knees of each animal for isotope incorporation studies.

#### PROGRESS

(5/84 - 9/84) No statistical difference was found between the normal saline, Ringer's lactate, and sterile water solutions. A paper has been written and will be submitted for publication.

STATUS: (C)

TITLE: The Evaluation of Synthetic and Autologous Grafts in an  
Acute Wound

PRINCIPAL INVESTIGATOR: COL Charles Andersen, MC

PROFESSIONAL ASSISTANTS: MAJ Eddie J. Reddick, MC  
Linda Bickerstaff, M.D., DAC

WORK UNIT NO: 83/65

#### TECHNICAL OBJECTIVE

to determine the most appropriate arterial replacement in an acute wound by comparing autologous saphenous vein, Gortex PTFE graft, and Meadox Biograft.

#### METHOD

Eighteen (18) adult mongrel dogs will be divided into three groups of six with each group having arterial replacement with either autogenous saphenous vein, Meadox Biograft, or Gortex PTFE Graft. After adequate general anesthesia, a standard, reproducible wound will be made in the hind leg near the area of the femoral artery using a captive bolt gun. The animals will be kept under anesthesia for three hours. The wounds will be debrided, the arterial graft will be inserted under sterile conditions, and the wound will be primarily closed. Blood cultures and wound cultures will be taken at the time of debridement and at the time of graft sacrifice. This will result in two aerobic and two anaerobic blood cultures and two aerobic and two anaerobic tissue cultures being performed on each animal. The wound will be observed daily for ten days and weekly thereafter for evidence of wound infection. At two months post injury, an arteriogram will be performed, the wound will be re-explored and the graft removed. The graft will be inspected for pseudoaneurysm formation, neointimal formation, obvious sites of breakdown, patency, and evidence of distal embolization. Animals which die prior to two-months will be autopsied and the graft will be inspected as above. If an animal becomes septic, it will be euthanized.

#### PROGRESS

7/83 - 9/84) This project was never started due to time constraints and then the ban on using dogs for research. It has been terminated.

STATUS: (T)

TITLE: Clinical Study of Viscoat™

PRINCIPAL INVESTIGATOR: COL Stanley Allison, MC

PROFESSIONAL ASSISTANTS: LTC John C. Goodin, MC  
MAJ Kevin J. Chismire, MC

WORK UNIT NO: 84/39

#### TECHNICAL OBJECTIVE

To prove the safety and efficacy of Viscoat™ sodium chondroitin sulfate-sodium hyaluronate in intraocular surgeries. Specifically, the investigation will ascertain Viscoat's ability to maintain anterior chamber depth and effectively protect ocular tissue.

#### METHOD

This is a group study under the sponsorship of CILCO, Inc. A minimum of twenty patients will be studied at MAMC. Each investigator will be asked to treat and submit patients consecutively, making an exception only when patients decline participation in the study in order to minimize physician bias. The control patient data were previously collected in a separate study and are appropriate for use in this investigation since the parameters measured are identical to those which will be evaluated in this study and patient groups being compared also match. The individual surgical procedures to be studied are as follows:

- a. Intracapsular cataract extraction with:  
anterior chamber lens implant
- b. Extracapsular cataract extraction with:
  - (1) anterior chamber lens implant
  - (2) posterior chamber lens implant
  - (3) secondary lens implant intraocular lens implantation as a secondary procedure following a prior cataract extraction.

Adult patients undergoing anterior segment intraocular lens surgery may be included in the study. Minors and patients experiencing intraocular infection will be excluded.

#### PROGRESS

The material did not arrive before the departure of COL Allison and LTC Goodin. Due to a shortage of qualified personnel to assume this protocol, it had to be terminated.

STATUS: (T)

TITLE: Implantation of Intraocular Lenses

PRINCIPAL INVESTIGATOR: COL Stanley C. Allison, MC

PROFESSIONAL ASSISTANTS: COL Stanley C. Sollie, MC  
LTC John C. Goodin, MC  
LTC Christopher G. Knight, MC  
MAJ Bruce D. Bellin, MC  
MAJ Kevin J. Chismire, MC  
MAJ Paul H. Ryan, MC  
CPT Lawrence E. Hannon, MC

WORK UNIT: 79/64

#### TECHNICAL OBJECTIVE

To become proficient in intraocular lens implantation and to gain investigator status with FDA requirements, thereby providing a new technique in ophthalmic surgical care for our patients.

#### METHOD

1. Obtain appropriate instruments to accomplish the procedure.
2. Obtain research investigator status with companies that have FDA approval to supply the lenses.
3. Implant lenses in 10 rabbits as a training experience for surgical nurses and assistants in this procedure.
4. Implant lenses in appropriately selected patients in order to provide visual rehabilitation.
5. To eventually establish this as a routine procedure in the military medical armamentarium of ophthalmic care.

#### PROGRESS

(82 10 - 83 09) Lenses were implanted in 86 patients in FY 84 with no adverse reactions.

STATUS: (O)



D E T A I L   S H E E T S  
F O R  
P R O T O C O L S

DEPARTMENT OF SURGERY

TITLE: Psychological Variables Related to Childbirth and Early Infant Development

PRINCIPAL INVESTIGATOR: MAJ Anthony C. Zold, MSC

PROFESSIONAL ASSISTANTS: CPT Richard H. Rubes, MSC  
CPT (USAR) Maren Stavig, ANC

WORK UNIT NO: 81/59

#### TECHNICAL OBJECTIVE

To study selected psychological and behavioral variables during pregnancy which may affect ease of delivery, medical complications, and early growth and development of the infant. Specifically, the independent variables to be investigated are: (1) maternal expectations of delivery and of the infant; (2) mother's perception of the husband's emotional support; (3) orgasmic history of the mother; (4) participation in various childbirth preparation programs; and (5) significant depression during pregnancy.

#### METHOD

Obtain interview and depression scale data from volunteers at 30-36 weeks gestation. After the birth, recontact mother for a brief follow-up interview to obtain mother's subjective rating of the delivery and the infant. Conduct record search for selected variables: length of labor, presence of complications, status of newborn, and the bonding rating between mother and child. At the 2-month well-baby follow-up visit, request mother to repeat the Zung Self-Rating Depression Scale and do a record search on the development of the infant. Data analysis will include descriptive statistics, correlation, and contingency table analysis.

#### PROGRESS

Initial data collection has been completed and is now being analyzed. The investigators are conducting a two-year follow up in those patients who are available.

STATUS: (O)

TITLE: Psychological, Parental, and Environmental Factors  
Related to the Developmental Level of the Child

PRINCIPAL INVESTIGATOR: CPT Vladimir Nacev, MSC

PROFESSIONAL ASSISTANTS: MAJ Glenn Tripp, MC  
MAJ Anthony Zold, MSC  
Christian Rubio, B.S.

WORK UNIT NO: 84/32

#### TECHNICAL OBJECTIVE

To study the relationship between child abuse potential as measured by the Child Abuse Potential Inventory (CAP-I); preventive factors such as stress, parenting skills, parent-child interactions, and support system variables (as measured by a questionnaire); and developmental level of the child (as measured by the Vineland Adaptive Behavior Scale).

#### METHOD

The research data will be collected from research volunteers who, at the present, have a 2 year old child. Approximately 50 subjects will be needed.

A brief questionnaire covering demographic and selected psychosocial variables, the CAP-Inventory, the Vineland Adaptive Behavioral Scale, and the Bayley Infant Development Scale will be administered.

Statistical analyses will include descriptive statistics and correlations (Pearson-r), ANOVA, and contingency table analysis (chi-square) on the demographic variables, the preventive factors, the child abuse potential, and the developmental variables.

#### PROGRESS

Data have been collected and analysis is underway. The final results should be available in two to three months.

STATUS: (O)

TITLE: The Neuropsychological Correlates of Hyperthyroidism  
and Its Treatment

PRINCIPAL INVESTIGATOR: MAJ Lloyd I. Cripe, MSC

PROFESSIONAL ASSISTANTS: LTC Gary Treece, MC  
MAJ Louis Pangaro, MC  
MAJ Raymond Parker, MC

WORK UNIT NO: 81/75

#### TECHNICAL OBJECTIVE

To determine the neuropsychological correlates of hyperthyroidism and the effects of treatment.

#### METHOD

Approximately 30 subjects presenting with a diagnosis of spontaneous hyperthyroidism, whose management and treatment have been decided by the primary physician, will be entered in the study. Phase I - will include the administration of the entire Halstead-Reitan Neuropsychological Test Battery during the physician's initial diagnostic work-up. Phase II - Patients will be randomly assigned to receive either propranolol, 40 mg q.i.d. or a placebo. After 7-10 days of drug therapy patients will again be given the Halstead Reitan Battery and blood levels will be checked. Phase III - the test battery will be administered for the third time after the patient has been euthyroid for one month as determined by TFT. Thirty controls without psychiatric, neurological, or thyroid disease will be matched with the experimental group for age, sex, intelligence, and education. They will be administered the Halstead-Reitan Battery on the same schedule as the experimental group. Thyroid status would be determined at each testing by blood levels for hormones. Hotelling's Multiple t-tests for multivariate data will be utilized to make comparisons between the groups for the three testings. Correlations with test measures and blood levels will also be made.

#### PROGRESS

(4/81 - 9/84) Four subjects were entered in this protocol and given either Inderal or a placebo without difficulty. This study has been terminated due to a lack of subjects and a lack of ancillary support to perform the neuropsychological studies.

STATUS: (T)

DETAIL SHEETS  
FOR  
PROTOCOLS

DEPARTMENT OF PSYCHIATRY

TITLE: Descriptive Study of Characteristics of Adolescent Women Who Have Had Unplanned Pregnancies with a Comparison Study of Those Who Have Not

PRINCIPAL INVESTIGATOR: LTC Gentry Yeatman, MC

PROFESSIONAL ASSISTANTS: Juvann M. Wolff, R.N.

WORK UNIT NO: 83/80

#### TECHNICAL OBJECTIVE

To identify the high risk and the low risk parameters for teenage pregnancies in order to better educate teenage girls in the area of avoiding unplanned pregnancies.

#### METHOD

A minimum of 100 adolescent women ages 14-19 will be provided with a cover letter and a questionnaire. A quiet, private location will be provided in which to complete the questionnaire.

After completion, the questionnaire will be placed in a sealed envelope by the participant and returned to the researcher or receptionist. The questionnaires will be collected and analyzed.

The questionnaire consists of 32 items, divided into eight categories: demographic, attitude toward contraception, knowledge of contraception, reproductive knowledge, perceived severity, perceived susceptibility, perceived benefits of action, and a self-esteem scale.

#### PROGRESS

The data collection phase is complete, but analysis of the data has not begun.

STATUS: (O)

TITLE: Prophylactic Intravenous Immunoglobulin in High Risk Neonates

PRINCIPAL INVESTIGATOR: MAJ Bruce E. Willham, MC

PROFESSIONAL ASSISTANTS: LTC Gary Pettett, MC  
MAJ Robert V. Jarrett, MC  
CPT Virginia Hallinan, MC

WORK UNIT NO: 84/37

#### TECHNICAL OBJECTIVE

To evaluate the effectiveness of intravenous immunoglobulin (IVIG) with high titer to known disease producing types of Group B streptococci (GBS) in preventing GBS disease in the high risk neonate.

#### METHOD

This will be a double-blind group study with prescreened IVIG and control drug (5% albumin) supplied to each institution in a pre-randomized fashion. Subjects will be neonates >2000 grams or 34 weeks at birth and >12 hours of age. Infants of mothers with immune deficiency syndrome will be excluded. The drugs will be as a single infusion, 500 mg/kg. All infants will have constant temperature, heart rate, respiratory rate, and blood pressure (if on umbilical arterial catheter) monitoring. If umbilical arterial catheter is not present, BP will be obtained before, midway through, and at the completion of the infusion. Fifteen-minutes post-infusion a whole blood sample for serum total of IgG and GBS antibody will be obtained. At 1, 2, and 8 weeks, another blood sample will be taken for antibody studies, a history will be recorded, and routine development assessment will be done.

#### PROGRESS

The investigators have only recently received notification of final approval from HSC. This is a multicenter project with USUHS/WRAMC being the coordinating center. They are still working on final details of the mechanics of the project. It is estimated that it will be 2-4 months before the actual investigation with patients begins.

STATUS: (O)

TITLE: The Coping Process of Families of Children with Birth Defects

PRINCIPAL INVESTIGATOR: MAJ Glenn C. Tripp, MC

PROFESSIONAL ASSISTANTS: William N. Friedrich, Ph.D.  
Lorna T. Willturner, Ph.D. (Candidate)  
Joyce Shaffer, Ph.D.

WORK UNIT NO: 84/11

#### TECHNICAL OBJECTIVE

To explicate the relationship of stress and various moderator variables to familial functioning and adaptation in families of children with birth defects.

#### METHOD

This will be a multimodal study of parents of 1,000 children with birth defects, done in conjunction with five other institutions. Each of the parents will complete a survey assessing their coping resources and perceived outcome. In addition to the basic survey, the following procedures will be utilized with subsamples of the total population: 150 subjects will be compared with families of children who manifest no noticeable disability; a group of 100 subjects will be compared to a control group of 100 subjects having a new baby with no handicap, matched as to father's rank, number of children in the family and parental education; selected index and control families will be compared at the beginning and end of the study period to evaluate the effects of longitudinal changes in family composition and function; additional ratings on 150 subjects will be completed by primary care personnel at the treatment institution and thus provide multimodal assessment of these families; a 12-month follow-up questionnaire will be administered to 150 selected families; problem solving interviews with 60 mothers will be conducted; 100 families who received the questionnaire prior to the formal diagnosis of birth defects will receive a 9-month, 12-month, and 18-month post diagnosis follow-up questionnaire, the assessment of change in these families being especially significant in understanding both the coping process during the time period immediately following the crisis and the effect of differential professional involvement on the family's coping during this crucial phase; and additional commonly utilized self-report instruments will be administered to 150 parents. The disabilities of the index cases will be rated by the severity of impairment on a scale of mild, moderate, or severe in nature.

#### PROGRESS

Ten subject families have been entered at MAMC. There was a delay in entering subjects due to approval procedures at some of the cooperating institutions.

STATUS: (O)



TITLE: Screening of Infants for Movement Deficits

PRINCIPAL INVESTIGATOR: LTC Jane K. Sweeney

PROFESSIONAL ASSISTANTS: COL Carl Plonsky, MC  
MAJ Gleen Tripp, MC  
Catherine Yokan, M.D.  
Lynette S. Chandler, Ph.D.  
Margon B. Holm, Ph.D.

WORK UNIT NO: 84/62

#### TECHNICAL OBJECTIVES

To establish norms for the Chandler Movement Assessment of Infants Screening Test (CMAI-ST); to establish inter-rater reliability, test-retest reliability, and predictive validity for the CMAI-ST.

#### METHOD

Fifty infants will be examined in age groups of 2, 4, 6, and 8 months, plus or minus one week. The infants will be examined in only one of those time frames in order to establish norms. Thirty infants from the 200 will be observed by two examiners simultaneously to determine inter-rater reliabilities. An additional 30 infants will be examined during two time frames to establish test-retest reliability. The outcome of the CMAI-ST will be correlated with physician assessment at the regularly scheduled 12-month exam to establish predictive validity. Half of the children from each group will be male and half will be female and distinct races will be represented to match the population of infants of military personnel. A Denver Prescreening Development Questionnaire will be completed by the parents. The high risk profiles of the 30 infants tested twice for test/retest reliability will be compared with those infants tested once. Only those twice-tested infants who maintain a high risk profile or increase their apparent degree of involvement will be considered at risk. All once-tested infants will be evaluated on their original profile. Pearson-product-movement correlations will be calculated to determine the predictive validity of twice-tested and once-tested infants. Percent of false positives and false negatives from each group will also be calculated.

#### PROGRESS

This study remains in progress. The number of subjects tested (89) is still too small to draw descriptive data for standardization purposes. The primary efforts at this point are directed toward filling in subjects at the 8 month age category. Early evidence indicates that a marked variation of movement patterns exists in normal subjects at 2 and 3 months. This supports clinical judgement that assessment for mild movement deficits is difficult to substantiate in infants before 4 months of age.

STATUS: (O)

TITLE: Use of Folinic Acid in Prevention of Neutropenia and  
Thrombocytopenia Secondary to Trimethoprim-sulfamethoxazole.

PRINCIPAL INVESTIGATOR: CPT Merlin L. Robb, MC

PROFESSIONAL ASSISTANTS: LTC Alan D. Mease, MC  
CPT Joseph High, MSC  
CPT G. William Letson, MC  
CPT Philip L. Rogers, MC

WORK UNIT NO: 82/38

#### TECHNICAL OBJECTIVE

To establish whether or not folinic acid can significantly reduce reported incidence of 34% neutropenia and 12% thrombocytopenia in children treated with Trimethoprim-sulfamethoxazole.

#### METHOD

Pediatric patients diagnosed as having acute otitis media or urinary tract infections would be treated with Trimethoprim-sulfamethoxazole (T-S) in one group and T-S plus folinic acid in a second group. Dosage would be 40 mg/kg per day for T-S and 0.5 mg/kg per day for folinic acid divided in two daily doses and given over a ten day period. Patients would be randomized and selected to be in one or the other group with the T-S plus folinic acid as an experimental group. Drugs would be given in such a fashion as to achieve a double blind study. Results would be obtained by drawing a baseline CBC and another on the final day of treatment. Anyone developing neutropenia would be followed further with CBC's until resolution of neutropenia. Count of medication left over would be undertaken at the end of treatment to determine compliance level. The final step would be statistical analysis of data. A minimum of 30 subjects would be studied in each group.

#### PROGRESS

(3/82 - 7/84) Cpt Robb assumed the role of principal investigator in October 1983 upon the departure of CPT Letson. Fifteen patients in the folinic acid group and 14 patients in the control group completed the study. All had a satisfactory clinical response to TMP-SMZ therapy. Compared to controls, patients in the experimental group had a less severe decline in ANC and WBC with a lower incidence of ANC on the final CBC. In addition, control patients developed a statistically significant decline in platelet count while experimental patients did not. It appears that folinic acid can ameliorate the decline in absolute neutrophil counts associated with oral TMP-SMA without altering its clinical efficacy. A paper was presented at the TriServices Pediatric Conference in March 1984.

STATUS: (C)

TITLE: Treatment of Recurrent Otitis Media: Chemoprophylaxis  
Versus Tympanostomy Tubes

PRINCIPAL INVESTIGATOR: MAJ James E. Arnold, MC

PROFESSIONAL ASSISTANTS: CPT James B. Erhart, MC  
CPT Alan G. Getts, MC  
CPT Stephen R. Pratt, MC

WORK UNIT NO: 83/33

#### TECHNICAL OBJECTIVE

To compare the effectiveness of treatment with PE tubes or antibiotic prophylaxis in children with recurrent otitis media.

#### METHOD

Children with recurrent otitis media will be randomly assigned to:

Group A: Bilateral myringotomies with placement of PE tubes.

Group B: Prophylactic antibiotic regimen consisting of Gantrisin, 500 mg for six months.

Group C: A placebo will be given for six months.

They will be followed for six months to determine the most effective treatment modality.

During an episode of acute otitis media, patients will be treated with appropriate antibiotics, and the study medicine will be discontinued until the episode is resolved.

A failure will be defined as two or more episodes of recurrent otitis media within a three month period after entering the study. Those patients who fail will be treated in the following manner:

Patients in Group A will be treated with the Gantrisin regimen. Patients in Groups B & C will then undergo myringotomy and PE tube placement.

#### PROGRESS

Ten additional subjects were entered in FY 84 for a total of 25. Patients are still being entered. There was one case of gastrointestinal upset while on medication which resolved when the medication was stopped.

STATUS: (O)

TITLE: The Effect of Dimethyl Sulfoxide on the Uptake of Cisplatin  
From the Urinary Bladder of the Dog

PRINCIPAL INVESTIGATOR: LTC William Belville, MC

PROFESSIONAL ASSISTANTS: LTC Samuel J. Insalaco, MC  
LTC George S. Ward, VC  
MAJ Eduardo S. Blum, MC  
MAJ Carl F. Cricco, MC  
MAJ Willis H. Jacob, MSC  
MAJ Roger Schoenfeld, MC

WORK UNIT: 79/57

NOTE: Thio-TEPA was the original drug to be utilized in this study. Being unable to develop a successful thio-TEPA assay, cisplatin was used in the study due to the ease of measurement by atomic absorption spectrometry and because its medium-sized molecular weight avoids excessive absorption. The original protocol is listed below.

#### TECHNICAL OBJECTIVE

Thio-TEPA has been used in the management of various types of neoplasias for almost two decades. However, its use in the management of urinary bladder carcinoma has had mixed results. In addition, the cytotoxic effect of thio-TEPA on the hematopoietic tissues are a severe side effect in its use. The objective of this study is to determine if intravesicular thio-TEPA can be more effectively transported through the urinary bladder wall using DMSO as a carrier.

#### METHOD

Ten dogs will be divided into groups I and II (4 dogs each and Group III (2 dogs). The test solution (50 ml) will be instilled into the urinary bladder of each animal and maintained there for one hour. The test solutions are: Group I 45 mg thio-TEPA in 50% DMSO; Group II - 45 mg thio-TEPA in an isotonic salt solution; and Group III - 50% DMSO in an isotonic salt solution. The Group III animals are to verify that DMSO does not interfere with thio-TEPA identification.

Blood samples will be obtained from the caudal vena cava and the external jugular vein immediately before instillation of the test solution and at 5, 10, 20, 40, and 60 min after instillation. One blood sample will be taken from a small vein on the bladder surface at 15 min and the test solution will be withdrawn from the bladder at 60 minutes.

## The Effect of Dimethyl Sulfoxide - Belville

Two dogs from Groups I and II will be studied for toxicity following a complete treatment regime, consisting of four weekly treatments as described above. These animals will have bone marrow, liver, kidney, and spleen biopsies before the first treatment. One week following the last treatment, the dogs will be sacrificed and tissue sections of the same organs plus the urinary bladder and lens will be taken. These tissues will be examined histopathologically for evidence of toxic changes. Complete blood counts will also be performed at weekly intervals.

The remaining two dogs in Groups I and II will have a section of urinary bladder removed following the test solution instillation. This tissue section will be divided and one part homogenized and extracted for thio-TEPA analysis and the other section evaluated histopathologically.

The withdrawn test solution, blood samples, and bladder tissue extracts will be analyzed by spectrophotometry to determine levels of thio-TEPA. The results will be compared to determine effectiveness of DMSO in increasing absorption of thio-TEPA.

### PROGRESS

Cis-platinum was used in this study rather than Thio-TEPA. The results of the study suggest that DMSO is useful by transporting cis-platin into the muscle layer of the canine bladder. Serum levels of cis-platin can be monitored and dosages can be adjusted to avoid untoward side effects with an acceptable assay. A larger series is necessary to solidify and extend these observations. No laboratory work was done in FY 84 due to personnel shortages and the ban on the use of dogs by DA. It is anticipated that further work will be accomplished in FY 85.

PRESENTATION: Schoenfeld, R.H., Belville, W.D., Jacob, W.H., Buck, A.S., Dresner, M.L., Insalaco, S.J., and Ward, G.S.: The Effect of Dimethyl Sulfoxide on the Uptake of Cisplatin From the Urinary Bladder of the Dog. Kimbrough Urologic Seminar, Denver, November 1981.

PUBLICATION: Schoenfeld, R.H., Belville, W.D., Jacob, W.H., Buck, A.S., Dresner, M.L., Insalaco, S.J., and Ward, G.S.: The Effect of Dimethyl Sulfoxide on the Uptake of Cisplatin From the Urinary Bladder of the Dog: A Pilot Study. J Amer Osteopath Assoc 82: 570-753, 1983.

STATUS: (Suspended)

TITLE: Orchiectomy and Observation in the Treatment of Clinical Stage I Nonseminomatous Germ Cell Tumor of the Testis (NSGCTT)

PRINCIPAL INVESTIGATOR: LTC William D. Belville, MC

PROFESSIONAL ASSISTANTS: COL Alfred S. Buck, MC  
COL Frederick H. Stutz, MC  
LTC Victor J. Kiesling, MC

WORK UNIT NO: 84/51

#### TECHNICAL OBJECTIVE

To determine the efficacy of orchiectomy alone in the treatment of clinical Stage I NSGCTT. The factors that predispose to relapse with Stage I disease will be analyzed.

#### METHOD

At present, clinical Stage I NSGCTT is treated by radical orchiectomy and radical retroperitoneal lymph node dissection. In order to avoid the ejaculatory impotence associated with the radical retroperitoneal lymph node dissection, the investigators propose to follow orchiectomy patients monthly for two years and then quarterly for two years with no further treatment unless relapse occurs. Subjects must have histologically confirmed carcinoma (not pure seminoma nor pure choriocarcinoma) at the testis. Post-orchiectomy evaluation must have been completed within four weeks of the diagnosis of the primary tumor. Patients with involvement of the spermatic cord or evidence of epididymal invasion; evidence of tumor outside the testis by any other diagnostic means; or a second malignancy (except a squamous or basal cell skin cancer) will be excluded. Patients who after careful counselling elect to undergo a radical retroperitoneal lymph node dissection will be followed as per protocol. Pre-orchiectomy evaluation will include complete history, physical, WBC and platelet count, HGB, bilirubin, alkaline phosphatase, SGOT, SGPT, serum calcium, BUN, creatinine, uric acid, chest x-ray, and serum tumor markers to include  $\alpha$ -fetoprotein,  $\beta$ -Hcg, and LDH. Post-orchiectomy evaluation will include bipedal lymphangiogram, abdominal and chest CT, excretory urography, and normal serum tumor markers which have returned to normal at a rate predicted by the known serum half-life of the respective marker. Patient follow-up will include history, physical exam, SMAC 20, CBC with platelet count, chest x-ray or CT, and serum tumor markers. During the first two years of follow-up, the patient will undergo abdominal CT every three months, and then annually for two additional years.

#### PROGRESS

There were no patients available for this protocol in FY 84.

STATUS: (O)

TITLE: A Protocol to Compare Segmental Mastectomy and Axillary Dissection With and Without Radiation of the Breast and Total Mastectomy and Axillary Dissection.

PRINCIPAL INVESTIGATOR: COL Preston Carter, MC

PROFESSIONAL ASSISTANTS: COL Stanley C. Harris, MC  
LTC James F. Bascom, MC  
LTC Dick R. Smith, MC

WORK UNIT NO: 82/02

#### TECHNICAL OBJECTIVE

To begin participation by MAMC in an established national cooperative study comparing the survival, treatment failure, and cosmetic results of partial mastectomy with and without radiation compared to modified radical mastectomy.

#### METHOD

Patients with breast cancers under two inches in size and without fixation to the chest wall or skin will be offered randomization to three treatment arms: (a) segmental mastectomy, axillary dissection; (b) segmental mastectomy, radiation, axillary dissection; (c) total mastectomy, axillary dissection. Patients with positive axillary nodes will, regardless of the primary treatment, be given L-PAM and 5-FU chemotherapy as further treatment.

#### PROGRESS

(9/81 - 2/84) Eight patients at MAMC were entered into the study. This national cooperative protocol with the National Surgical Adjuvant Breast Project was closed as of February 1984. The investigators continue to follow six of the patients who were entered.

STATUS: (C)

TITLE: Intravenous Dexamethasone to Control Post Operative Pain  
in Orthopedic Patients

PRINCIPAL INVESTIGATOR: CPT Michael Q. Cosio, MC

PROFESSIONAL ASSISTANTS: COL Richard Camp, MC  
LTC Thomas J. Parr, MC  
MAJ Douglas Beirne, MC

WORK UNIT NO: 82/29

#### TECHNICAL OBJECTIVE

To determine whether intravenous dexamethasone can decrease the severity of post-operative pain in orthopedic patients.

#### METHOD

Patients undergoing elective surgery will be studied with the following exceptions: history of altered immune response or delayed wound healing; steroid use in past 6 months; open wounds or fractures, infected wounds/joints or abscesses; open growth plates; total joint, hip, and spine surgery, history of malignancy; pregnant or lactating female. In a prospective, randomized, double-blind study, dexamethasone or placebo (D5W) will be given IV slow push in 3 doses: 12 mg in the OR prior to surgery, then 4 mg 6 hours and 14 hours after the first dose. The patient will fill out a questionnaire regarding his pain level throughout the hospital stay. Pain medications will be standardized as follows: Morphine 4 or 8 mg IM q 3 hr and codeine 30 or 60 mg po q 4 hr prn pain. If allergic to codeine, Zomax 1 or 2 tabs po q 4 hr prn will be used. If allergic to morphine, Stadol 1 or 2 mg IM q 3 hr with Zomax will be used. The use of antipyretics and salicylates will be withheld for one week to insure detection of fever and possible infection as early as possible. Since some surgery is more painful than others, the patients will be subdivided into groups by regions of pain. Patients will be followed until the sutures are removed, usually two weeks later.

#### PROGRESS

(2/82 - 9/84) Eighty patients were entered in FY 84 for a total of 130 subjects. The data collection is complete and the data are currently being analyzed. No adverse reactions were identified.

STATUS: (C)



TITLE: Incidence and Natural History of Deep Venous Thrombosis  
in Patients Undergoing Elective Knee Surgery

PRINCIPAL INVESTIGATOR: CPT Michael Q. Cosio, MC

PROFESSIONAL ASSISTANTS: COL Stanton Brown, MC  
COL Joel Sim, MC  
LTC Thomas J. Parr, MC  
Denise Anderson, R.N.

WORK UNIT NO: 82/57

#### TECHNICAL OBJECTIVE

To determine the true incidence, natural history, and response to therapy and prophylaxis of DVT in patients undergoing elective knee surgery.

#### METHOD

Approximately 100 patients undergoing elective surgery about the knee, except for knee ligament reconstruction, total knee replacement, or pediatric patients, will have daily clinical evaluation for DVT and PE following surgery. If a patient develops signs and symptoms of DVT or PE, an immediate Doppler and venogram and/or lung scan will be performed as appropriate. Otherwise, a venogram will be performed following a Doppler evaluation of both limbs 7-10 days post op. If the incidence of DVT in the nonoperated leg is found to be <5%, venography will be done only on the operated leg. Those patients who have DVT will undergo a perfusion lung scan immediately after the venogram, at four and eight days after detection of the DVT. Those who have CVT confined to the calf will not receive any therapy. Those with DVT of the calf with proximal extension will receive a 10 day course of IV heparin. The heparin will always be given by continuous IV infusion, maintaining the PTT between one and a half to two times normal.

#### PROGRESS

(2/82 - 4/84) This study was terminated because the investigators found that the 30 subjects who had been entered reflected less than 10% of the number of patients undergoing elective knee surgery. Hence, any conclusions drawn would not be valid. Multiple attempts by the principal investigator to have other residents enter their patients were unsuccessful.

STATUS: (T)

TITLE: Scrotal Blood Flow Following Shouldice Herniorrhaphy

PRINCIPAL INVESTIGATOR: CPT Rodney Davis, MC

PROFESSIONAL ASSISTANTS: COL Stanton Brown, MC  
COL Alfred S. Buck, MC  
MAJ Eddie Reddick, MC  
CPT Mark Ludvigson, MC

WORK UNIT NO: 84/35

#### TECHNICAL OBJECTIVE

To determine the normal scrotal blood flow following inguinal herniorrhaphy in the adult male.

#### METHOD

Patients undergoing routine inguinal herniorrhaphy will be asked to participate in the study. Scrotal scans will be done within 3 days of surgery. One day postoperatively the patient will be re-scanned. If the scan is found to be abnormal, an additional scan will be done at the two week follow-up visit.

Nuclear Medicine Service personnel will interpret the scans without a clinical history in order to blind the interpreter.

Each member of the General Surgery Team will be given postoperative criteria to evaluate the patients. The criteria will include presence or absence of scrotal swelling, hematoma, and ecchymosis. The swelling will be graded 1+ (minimal), 2+ (moderate = 2 x NL), or 3+ (severe with tense testicle and tenderness). The pain will be graded 1+ (minimal requiring no medications for pain), 2+ (moderate p.o. pain medication) or 3+ (severe requiring IV or IM pain medications).

Clinical and nuclear scan data will be compared using  $X^2$  analysis.

After 25 patients have been studied, the data will be evaluated to determine if more patients need to be studied for statistical purposes.

#### PROGRESS

This study is on-going. Eight patients were entered in FY 84.

STATUS: (0)

TITLE: The Effects of the Shaw Scalpel on Wound Healing

PRINCIPAL INVESTIGATOR: CPT Milton B. Ellis, MC

PROFESSIONAL ASSISTANTS: COL William H. Gernon, MC  
MAJ Stanley P. Liebenberg, VC  
CPT Steve Koopmeiners, MC  
Alvin Novack, M.D.  
James Wells, M.D.

WORK UNIT NO: 84/42

#### TECHNICAL OBJECTIVE

To document how different temperatures of the heated (Shaw) scalpel affect canine and porcine skin incisions and to examine and compare wound breaking strength and histology.

#### METHOD

Six adult mongrel dogs and six weanling piglets will be used. The six dogs will be studied first to perfect techniques. The information obtained from the piglet work will be most representative of the effects of the Shaw scalpel on human skin because porcine and human skin have been shown to correlate closely histologically.

The backs of the animals will be shaved, surgically prepped, and two sets of 5 cm paramedian incisions will be made through the back skin using a #10 Bard-Parker scalpel blade, the Shaw scalpel at 88°C, and the Shaw scalpel at 119°C for a total of six incisions on each animal. The incisions will be closed with standard surgical staples to provide carefully controlled closures. The animals will be cared for in a routine and uniform manner. The animals' condition and the characteristics of their incisions will be monitored daily. The incisions will be photographed at regular intervals.

Two animals of each species will have excisions of all skin incisions at 7, 14, and 21 days post-operatively. These new skin incisions will receive primary closure with a nonabsorbable suture material placed in an interrupted pattern. One set of incisions will be examined histologically and the other set functionally. Those to be examined for function will have the wound breaking strength determined by a calibrated tensionmeter.

#### PROGRESS

Six dogs and six piglets were studied as planned. Analysis of the samples must be completed.

STATUS: (O)

TITLE: Sinusitis Secondary to Foreign Bodies in the Nasal  
Cavity and Its Relationship to Sepsis in the Severely  
Ill Patient

PRINCIPAL INVESTIGATOR: CPT James B. Erhardt, MC

PROFESSIONAL ASSISTANTS: COL Waylon Black, MC  
COL (Ret) Leonard Hays, MC  
MAJ William Fill, MC  
MAJ DelRay Maughan, MC  
MAJ Eddie Reddick, MC  
CPT Robert Holzman, MC

WORK UNIT NO: 84/23

#### TECHNICAL OBJECTIVES

To determine the incidence of sinusitis in severely ill patients who have nasotracheal tubes in place; to define which sinuses are commonly involved in these cases; to determine which organisms, may be involved; to determine whether CT examination provides more accurate and/or earlier diagnosis than conventional x-ray films in these cases; and to determine the correlation between roentgenographic evidence of sinusitis and clinical evidence of sepsis in these patients.

#### METHOD

A minimum of 50 patients with nasotracheal intubation tubes in place for >72 hrs have the following evaluation: physical exam of the head and neck; and plain x-ray films and CT exam of the paranasal sinuses. If the plain films or the CT scan demonstrates no sinus pathology, repeat films (plain films and CT films) will be obtained every 10-14 days while the nasotracheal tube remains in place. If the plain films or CT scan demonstrate opacification of the maxillary sinuses, antral punctures will be performed for aerobic and anaerobic cultures. If the plain films or CT scan demonstrates opacification of the ethmoid or sphenoid sinuses, attempts will be made to obtain bedside sinus cultures. When the patient's prognosis is such that an extended intubation is anticipated, consideration will be given to placement of a tracheostomy at which time the ethmoid and sphenoid sinuses will be concurrently cultured. If, at any time, a patient with a nasotracheal tube develops a picture of sepsis and no obvious source other than opacification of the sinuses is identified, the patient will undergo surgical decompression of the involved sinuses in the main operating room, with cultures obtained at that time.

#### PROGRESS

Patients are still being entered. Subject accumulation has been slow.

STATUS: (0)

TITLE: An Evaluation of the Safety and Efficacy of Cyanoacrylate Ester in Ossicular Reconstruction and Nerve Graft Anastomosis in the Guinea Pig Middle Ear

PRINCIPAL INVESTIGATOR: COL William H. Gernon, MC

PROFESSIONAL ASSISTANTS: CPT Roy Kim Davis, MC

WORK UNIT NO: 77/88

#### TECHNICAL OBJECTIVE

To determine the safety and efficacy of cyanoacrylate ester in the middle ear; specifically, for ossicular reconstruction for histological changes in the oval window area and in the facial nerve. In addition, the use of this compound in tympanoplasty would be a natural extension of this project. The intended purpose of this study is to open the door for the use of cyanoacrylate ester in human surgery, initially on an experimental basis.

#### METHOD

The investigators propose to use Histoacryl and Crazy Glue to do interpositions (incus) on a test group of guinea pigs as well as place glue on the facial nerve, perhaps to do facial nerve anastomoses, and to place the glue in the oval window area. Approximately 39 animals would be utilized. At 3, 6, and 12 months, 12 experimental animals and one control animal would be sacrificed. Histological temporal bone studies would then be conducted at AFIP.

#### PROGRESS

(9/77 - 9/84) Sixteen patients were entered in this protocol in previous years. Findings show that the cyanoacrylate causes considerable bony overgrowth. There is no evidence of toxicity to inner ear structures.

Due to time restraints, the investigators will do no further work on this protocol as had been planned.

PRESENTATION: Wells, J., Gernon, W.H., Ward, G.S., Davis, R.K., and Hays, L.L.: Otosurgical Model in the Guinea Pig (*Cavia porcellus*). American Academy of Otolaryngology, Head and Neck Surgery, Sep 81, New Orleans, LA.

STATUS: (C)

TITLE: Advanced Trauma Life Support Course

PRINCIPAL INVESTIGATOR: LTC Stanley C. Harris, MC

PROFESSIONAL ASSISTANTS: MAJ Stanley P. Liebenberg, VC

WORK UNIT NO: 83/08

#### TECHNICAL OBJECTIVE

To provide training to general surgery, emergency medicine, and family practice residents in proper management of the initial one hour after major trauma.

#### METHOD

This course as designed by the American College of Surgeons will be given at MAMC one to two times per year. The course involves hands-on training using dogs as the experimental model. Each student will be directly involved in the performance of a venous cutdown, cricothyroidotomy, tube thoracostomy, peritoneal lavage, and pericardiocentesis.

#### PROGRESS

Four courses were presented with 16 students in each class. All students felt the hands-on laboratory instruction was essential to the successful application of the ATLS knowledge.

The protocol has been terminated due to the ban on the use of dogs by DA. A protocol using a different animal model is planned.

STATUS: (T)

E: Medical Treatment of the Frey Syndrome

CIPAL INVESTIGATOR: COL Leonard L. Hays, MC

ESSIONAL ASSISTANTS: Alvin J. Novack, M.D.  
University of Washington

UNIT NO: 76/06

#### TECHNICAL OBJECTIVE

tudy objectively the true incidence of the Frey syndrome in -parotidectomy patients by means of the Minor Starch Iodine ; to determine the effect of, and patient satisfaction with, cal management comparing on a double blind basis topical use placebo, varying concentrations of scopolamine hydrobromide, the newer anticholinergic agent, glycopyrrolate; to investi- the value and practicality of iontophoresis of the above ts to increase the duration of satisfactory control of sweat- and to compare the topical use of a patient's most effective perspirant on the involved facial skin with the result from topical use of the most effective agent in the double blind es for that patient.

#### METHOD

e I - Double-blind treatment with 1/4%, 1%, and 3% scopolamine obromide cream, 0.1% glycopyrrolate, and a placebo; comparison he patient as to effectiveness; and retreatment after drug ge adjustment if the patient fails to respond.

e II Utilize iontophoretic introduction of the best anti- inergic agent to a group of volunteers with significant ting symptoms and to a group who are medical failures and are action and duration of action with iontophoretic intro- ion using tap water, Ringer's lactate, or saline.

e III - Patients who fail medical treatment or have become atisfied with the medical treatment and have significant toms confirmed on minor starch-iodine testing will be red surgery such as flap elevation or tympanic neurectomy. cal Treatment of the Frey Snyderome - Hays

#### PROGRESS

protocol has been closed at MAMC due to the retirement of Hays. He will continue the protocol with Dr. Novack through University of Washington, but no patients from MAMC will be ect.

e publications and one presentation came about as a result his protocol.

US: (C)

TITLE: Teaching Program for Practical Microsurgery

PRINCIPAL INVESTIGATOR: LTC Stanley Jackson, MC

PROFESSIONAL ASSISTANTS: COL Preston L. Carter, MC  
COL Leonard L. Hays, MC  
LTC Thomas G. Griffith, MC  
MAJ Stanley P. Liebenberg, VC

WORK UNIT NO: 82/35

#### TECHNICAL OBJECTIVE

To establish a formal training program in clinical microsurgery at MAMC for use of surgeons desiring to develop this expertise.

#### METHOD

In order to perfect the techniques needed to perform clinical microsurgery, extensive practice is needed in the research laboratory. The teaching program will be established at the Department of Clinical Investigation, and a room will be set aside for the project where equipment for the microsurgery can be housed. A schedule of two afternoons per week will be set aside for teaching sessions. Animal model preparations (cadaver and live) will be developed by the veterinary surgical consultant with the support of the clinical teaching staff. Sessions will begin with lectures, followed by practical exercises in anatomy and step-by-step instruction in the surgical techniques.

#### PROGRESS

(2/82 - 9/84) Due to the departure of the investigators, there was no action on this protocol in FY 84. It has been terminated.

STATUS: (T)



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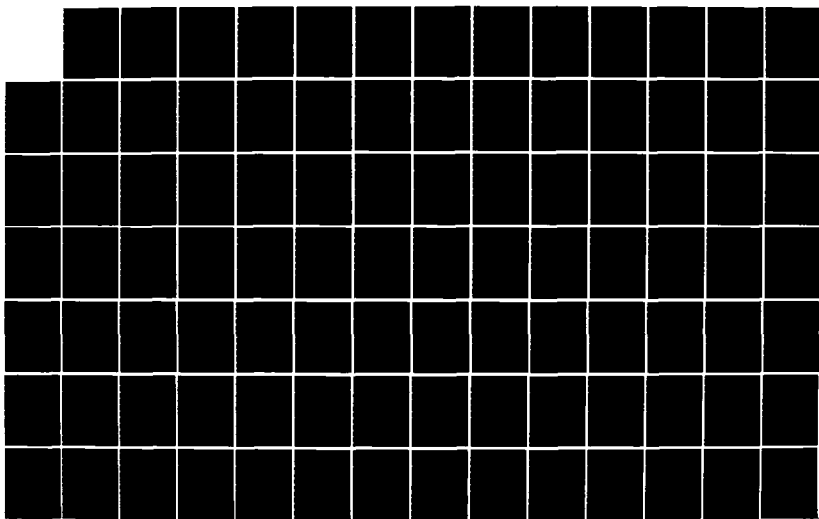
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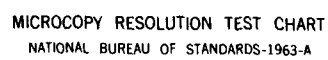
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NL





**TITLE: Reanastomosis of the Vas Deferens in the Canine Model  
Using Fibrin Glue**

**PRINCIPAL INVESTIGATOR: CPT James C. Mason, MC**

**PROFESSIONAL ASSISTANTS: LTC Victor J. Kiesling, Jr., MC  
CPT Rodney Davis, MC**

**WORK UNIT NO: 84/70**

#### TECHNICAL OBJECTIVES

To determine if the use of an inhibitor of fibrinolysis (Amicar) increases the tensile strength or alters the time of lysis of fibrin glue and to determine if the use of fibrin glue with reanastomosis of the vas deferens can improve the patency results of vasovasostomy compared to simple suture reanastomosis.

#### METHOD

Tensile strength of fibrin glue will be determined using the Ingstrom tensometer. Clots will then be tested for tensile strength. Clot lysis will be determined by observing the time interval from clot formation until clot liquefaction is apparent.

Bilateral vasectomy will be performed on 8 male dogs using the glue with the greatest tensile strength and longest dissolution time. Eight right anastomoses will be made; four with fibrin glue and four without. Two serosal sutures of 7-0 proline will be placed 1 cm on either side of the anastomosis for later measurement of possible dehiscence. Approximately one month after vasovasostomy a semen analysis will be obtained. The right anastomoses will then be surgically removed with a large segment of vas deferens and evaluated for patency and histopathological changes. Concurrent vasovasostomy will be performed on the left vas deferens, using glue on the dogs in the reverse order as before. The anastomoses will be removed and evaluated as before. Semen collections in each animal will be performed a minimum of 4 times - pre-vasectomy, post-vasectomy, and post-unilateral vasovasostomy with and without fibrin glue (unilateral anastomosis will be performed twice in each dog).

#### PROGRESS

No animals were utilized. This protocol was not started due to the ban on the use of dogs by DA. It will commence if and when the ban is lifted.

**STATUS: Suspended**

**TITLE:** Evaluation of Calcium Sulfate (Plaster of Paris) as  
an Alloplastic Implant in Mandible Reconstruction

**PRINCIPAL INVESTIGATOR:** MAJ Del Ray Maughan, MC

**PROFESSIONAL ASSISTANTS:** COL Leonard L. Hays, MC  
MAJ Stanley P. Liebenberg, VC  
CPT John H. McGath, MC  
CPT Wallace E. Taylor, MC

**WORK UNIT NO:** 82/34

#### TECHNICAL OBJECTIVE

To evaluate the use of calcium sulfate as an alloplastic implant material in reconstruction of surgical defects of the mandible.

#### METHOD

Six mongrel dogs will undergo unilateral partial mandibulectomies (2-4 cm segments of hemi-mandible, depending upon dog size) under endotracheal halothane anesthesia. Three will have periosteum preserved and three will have periosteum removed. Each dog will undergo immediate reconstruction utilizing calcium sulfate as an alloplastic implant. Stabilization will be accomplished utilizing standard ASIF fixation bone plates applied to the lateral aspect of proximal and distal segments. Each animal will be placed on liquids postoperatively until intraoral mucosa is sealed and then on a soft diet for four to six weeks. Each dog will be followed with monthly roentgenograms to determine calcium sulfate resorption and osteoneogenesis. Two dogs (one with periosteum intact and one with periosteum removed) will be sacrificed at two, four, and six months postop and the reconstructed mandibles examined histologically for bone formation.

#### PROGRESS

(3/82 - 9/84) Eleven animals were studied. Three of three of the experimental animals had non-union (teeth extracted at time of mandible reconstruction); 4/5 experimental animals had solid union with histologic confirmation of bone growth (teeth extracted six weeks prior to mandible reconstruction); 3/3 of the control animals had non-union (no mandible reconstruction).

**Conclusions:** canines can be used as a reliable animal model for mandible reconstruction if teeth are removed prior to resection/reconstruction and calcium sulfate appears to stimulate osteogenesis in mandible defects in a canine model.

A paper has been accepted for presentation at the Second Bone Grafting Symposim, sponsored by the Department of Plastic Surgery, UCSD, Dec 84.

**STATUS:** (C)

TITLE: Immunologically Mediated Persistent Infertility in  
Patients Following Vasovasotomy

PRINCIPAL INVESTIGATOR: LTC Michael R. Moon, MC

PROFESSIONAL ASSISTANTS: COL Stephen R. Plymate, MC  
LTC William E. Belville, MC  
LTC James W. Higbee, MSC

WORK UNIT NO: 82/68

#### TECHNICAL OBJECTIVE

To investigate the relationship between immunologically mediated infertility in patients after vasovasotomy and its treatment by corticosteroids.

#### METHOD

Thirty males who are going to have vasovasotomies performed will, prior to surgery, have serum samples analyzed for antisperm antibodies using the Isojima and Kibrick techniques as described by Linnet. They will have two serum samples measured at least one week apart. Following vasovasotomy, monthly semen analyses will be performed, and upon the first appearance of sperm in the ejaculate, serum and semen will be analyzed by the Isojima and Kibrick technique for antisperm antibodies. Monthly semen analyses will be followed, and, when sperm samples for two consecutive months are >20 million/ml with >20% motility, a sperm penetration assay (SPA) will be performed as well as a repeat antibody study. If the SPA is negative, patients will be treated with 1 mg dexamethasone three times a day for one month. One month following the dexamethasone treatment, a repeat SPA will be performed as well as serum drawn for antibodies. If the patient's spouse becomes pregnant during the study, serum and semen antibodies will be drawn and a SPA performed as soon as the pregnancy is recognized.

#### PROGRESS

No new patients were entered during FY 84. The principal problem has been finding patients who will be available for follow-up. The problem of obtaining adequate numbers of patients has been compounded by the fact that only a small percentage of patients who undergo vasovasostomy will be infertile after the procedure. Also, the number of patients undergoing vasovasostomy at Madigan has declined over the last year.

STATUS: (O)

**TITLE:** Cystoscopy Associated Bacteriuria and Its Prevention by Trimethoprim/Sulfamethoxazole (TMP/SMX)

**PRINCIPAL INVESTIGATOR:** LTC Michael R. Moon, MC

**PROFESSIONAL ASSISTANTS:** LTC William D. Belville, MC  
LTC Victor J. Kiesling, MC  
MAJ Brian J. Miles, MC  
LCDR Joseph A. Fernandez, MC  
CPT Rodney Davis, MC  
CPT James C. Mason, MC  
CPT Thomas A. Rozanski, MC  
Ray Hackett, M.D.  
Herbert C. Kennedy, M.D.

**WORK UNIT NO:** 84/43

#### TECHNICAL OBJECTIVES

To determine the incidence of cystoscopically induced bacteriuria following elective cystoscopy at MAMC and the VA Hospital, Seattle; to determine the risk factors for cystoscopy induced bacteriuria; and to determine the effectiveness of prophylactic precystoscopy trimethoprim (160 mg) and sulfamethoxazole (800mg) (TMP/SMX).

#### METHOD

This study will be a cooperative effort with Dr. Ray Hackett, Urology Svc, University of Washington. Dr. Hackett will provide a randomization list, placebos, and medication. Study patients (1000) will be adult patients undergoing elective cystoscopy. Patients excluded from the study: who have a history of allergy to TMP/SMX or its components; who have taken an antibiotic within 2 weeks of the study; who have additional procedures performed at cystoscopy; <18 years of age; pregnant patients; with a history of folate deficiency; and with severe glucose-6-phosphate dehydrogenase deficiency. The patients will be randomly assigned to either the TMP/SMX or a placebo group. A cystoscopy will then be performed and data recorded. Urine will be collected on three occasions for each patient; pre-cystoscopy and one day and one week post-cystoscopy. The incidence (percentage) of infection will be determined for both the control and treatment groups for their subcategories (age and pre-existing conditions) using chi square analysis.

#### PROGRESS

Eleven patients have been studied at MAMC with none contracting a urinary tract infection after cystoscopy. Dr. Hackett from the University of Washington reports that he has studied 60 subjects with no incidence of post-cystoscopy infection.

**STATUS:** (0)

**TITLE:** A Prospective Clinical Trial Comparing Drainage or no Drainage After Acute Cholecystectomy

**PRINCIPAL INVESTIGATOR:** CPT Michael J. O'Reilly, MC

**PROFESSIONAL ASSISTANT:** COL Preston L. Carter, MC

**WORK UNIT NO:** 82/58

#### TECHNICAL OBJECTIVE

To determine the long term sequelae of repair of peripheral meniscal tears.

#### METHOD

This study will be a randomized prospective clinical trial. Patients presenting with signs and symptoms consistent with acute cholecystitis to include right upper quadrant pain, fever, and leukocytosis will have diagnosis confirmed by histological examination of the gallbladder. Cholecystectomy will be performed according to standard technique through a subcostal incision. If the surgeon determines that the patient has no contraindications for inclusion in the study, the patient will be randomly assigned to have drainage of the gallbladder bed with a Jackson-Pratt drainage system brought out through a lateral stab wound or no drainage of the gallbladder bed. A bile culture will be taken and an intraoperative cholangiogram performed when possible. Visible bile in the peritoneal cavity following cholecystectomy, presence of a frank abscess cavity in the gallbladder bed, or a common bile duct exploration will be cause for exclusion from the study. Postoperative management and follow-up will be identical in both groups. Parameters to be followed include: postoperative fever, wound infection, return of gastrointestinal tract function, and length of stay in the hospital. A SMAC-20 will be drawn on all patients on postoperative day number two.

#### PROGRESS

(2/82 - 9/84) No patients have been entered in this study due to time constraints on the investigators and the study has been terminated.

**STATUS:** (T)

TITLE: Repair of Peripheral Meniscal Tears; A Long Term Study

PRINCIPAL INVESTIGATOR: LTC Thomas J. Parr, MC

PROFESSIONAL ASSISTANTS: CPT Michael Q. Cosio, MC

WORK UNIT NO: 82/45

#### TECHNICAL OBJECTIVE

To determine the long term sequelae of repair of peripheral meniscal tears.

#### METHOD

PATIENT POPULATION: Patients who have had symptoms of a torn meniscus for at least four months and who subsequently are found to have a peripherally torn meniscus. Patients will be excluded who have undergone a previous menisectomy, who have a torn anterior or posterior cruciate ligament, or who have worse than Grade II osseous arthritis.

If the meniscus is detached from its capsular attachment, it will be reattached with 2-0 Dexon suture going through the capsule, grabbing at least 1 mm of the body of the meniscus, then back out of the capsule and tied. If there is a tear of the body of the meniscus paralleling the capsular edge of the meniscus and leaving no more than 2 mm of meniscus still attached to the capsule, this capsular remnant will be excised, the edge of the meniscus will be abraded, and the meniscus reattached to the capsule as above. Both groups of patients will be placed in a long leg bent knee cast, partial weight bearing on crutches for six weeks before beginning knee rehabilitation. Follow-up will be every three months for the first year, six months the second year, then annually for subsequent years up to ten years. If the patient develops recurrence of the symptoms despite vigorous physical therapy and anti-inflammatory medication, he will be rearthroscoped for inspection of the repair. A final evaluation of the knee will be made at ten years that will include x-rays of the knees, assessment of the level of activity, and knee function.

#### PROGRESS

(4/82 - 9/84) Six patients were entered. Early evidence has shown in all of the centers studying this problem that repair is always indicated. This has become a standard procedure in orthopaedics.

STATUS: (C)



**TITLE:** Ultrasonic Localization of Internal Fixation Devices  
Within Connective Tissues

**PRINCIPAL INVESTIGATOR:** CPT Davis C. Peterson, MC

**PROFESSIONAL ASSISTANTS:** LTC Thomas J. Parr, MC  
MAJ William Fill, MC  
MAJ Stanley P. Liebenberg, VC

**WORK UNIT NO:** 83/75

#### TECHNICAL OBJECTIVE

To determine the feasibility of A-mode ultrasonography in determining the extent of hardware penetration during internal fixation procedures.

#### METHOD

**PHASE I:** A 3.5 MHz ultrasonic transducer with a rapid sweep oscilloscope monitor will be coupled through a glycerin contact with a machined 5/32" diameter stainless steel Steinman pin with 90° + 2 min faces via a machined brass jig incorporating an air chamber to minimize noise as well as shear wave interference in the near field and a 90° centered contact with respect to the transducer face. The exact length will allow calculation of the sound conduction velocity by measuring the time delay from initial to the reflected wave from the distal face. The reflected wave form characteristics will also be determined. The initial phase will be conducted in air and fluid media. A stainless steel reflector plate will then be positioned at 1 mm increments from the pin tip in a saline bath to determine the effect of acoustic impedance and beam attenuation on the reflected waveform. An attenuation coefficient will be determined as a reference for tissue comparison. Connective tissue samples will then be interposed to again determine the wave patterns and attenuation coefficients. Should the bone/metal acoustic impedance interface difference be too great to allow resolution of reflected waves from bone media through stainless steel, metals such as vitallium and titanium with density and elastic moduli nearer that bone will be used.

**PHASE II:** Phase I will be repeated using machined pins with 45° tetrahedral tips and 90° faces with precise length measurements with the intent of maximizing the amplitude of the reflected wave and minimizing base width in a cutting tip.

**PHASE III:** Clinical feasibility will be determined by using previously designed and tested hardware in an articular tissue block stratified with perpendicular planes of cancellous bone, subchondral bone, and articular cartilage. Correlation of the strata level by direct mapping of a cross section will be compared with depth measurement determined directly from a machined nylon core guide. Patterns of reflection will be recorded in the previous manner with progressive advancement of the pin to correlate wave form with level of penetration.

#### PROGRESS

The data have been collected and will be analyzed within the next few months.

**STATUS:** (O)

**TITLE:** Canine Training Model for Endoscopic Laryngeal Surgery  
Using the CO<sub>2</sub> Laser

**PRINCIPAL INVESTIGATOR:** CPT Wallace E. Taylor, MC

**PROFESSIONAL ASSISTANTS:** COL Leonard L. Hays, MC  
MAJ Stanley P. Liebenberg, VC  
MAJ Del Ray Maughan, MC

**WORK UNIT:** 82/55

#### TECHNICAL OBJECTIVE

To train ENT residents in the use of the CO<sub>2</sub> laser in a non-human subject in a controlled setting simulating a human situation prior to performing in an actual clinical setting.

#### METHOD

Twelve large mongrel dogs will be anesthetized with ultra-short acting barbiturate and placed in dorsal recumbancy. Suspension laryngoscopy will then be employed to visualize the larynx. ENT residents will use the CO<sub>2</sub> laser to perform a partial laryngectomy. Supplemental oxygen will be administered to the animal using the Saunders jet ventilating device to displace CO<sub>2</sub> from the lower airways and to facilitate viewing of the operative site during actual tissue removal with the laser. The opposite hemilarynx will be left unoperated to serve as a control. Each dog will be placed on a liquid diet for 24 hours post-op and will then be fed a semi-soft diet for the next 5 days. Each dog will be endoscoped at weekly intervals until healing is completed. The dogs will then be used in conjunction with the protocol "Use of the CO<sub>2</sub> Laser in Pharyngeal Surgery in the Dog"; LTC Stanley P. Liebenberg, Principal Investigator.

#### PROGRESS

No work was done on this protocol during FY 84 due to the departure of several of the investigators. Dr. Maughan has requested that the protocol remain open and it will be completed under the direction of MAJ Gregory Garth, MC, if the ban is lifted on the use of dogs by DA.

**STATUS:** Suspended

DETAIL SHEETS  
FOR  
PROTOCOLS

NUTRITION CARE DIVISION

**TITLE:** Determining and Redefining Nutrition Terms Which Are Unfamiliar to Adults

**PRINCIPAL INVESTIGATOR:** MAJ Diana M. Barefoot, ASMC

**PROFESSIONAL ASSISTANTS:** Lou Kupka, B.S.N.

**WORK UNIT NO:** 84/16

#### TECHNICAL OBJECTIVES

To determine if defining nutrition terminology in a piece of nutrition education material increases the learners understanding of the material and to assess the comprehension of the nutrition education material in subjects aged 18-28 and over age 61.

#### METHOD

**STUDY SAMPLE:** 100 subjects aged 18-28 who are soldiers from Ft Lewis and 100 subjects aged 61 and over from three Seattle senior centers. Men are the preferred subjects, but both sexes will be tested. Correct age and willingness to participate in the study are the only criteria for patient selection.

There will be four informational sheets containing varying degrees of definition of terms. One of the sheets will be distributed randomly to each subject. The subject will be asked to read the information sheet, the sheet will be collected from the subject, the subject will be tested on the information contained on the sheet, and the proportion of correct answers calculated and comparisons made. Age, sex, and amount of education will be a part of the statistical considerations.

#### PROGRESS

This study has been completed. A thesis has been written by Ms Kupka and submitted to her committee at the University of Washington. A copy of the paper will be forwarded to the Department of Clinical Investigation; however, no information on the results of the study is available at this time.

**STATUS:** (C)

**TITLE:** Assessment of the Impact of the Weight Program at  
Fort Lewis and MAMC

**PRINCIPAL INVESTIGATOR:** 1LT Cecilia M. Dewinne, AMSC

**PROFESSIONAL ASSISTANTS:** COL Stephen R. Plymate, MC  
MAJ Diana M. Barefoot, AMSC  
CPT Karl E. Friedl, MSC  
1LT Rogan L. Taylor, AMSC

**WORK UNIT NO:** 84/30

#### TECHNICAL OBJECTIVES

To determine if there is a need for additional weight loss assistance for troops in the weight loss program for Ft Lewis and MAMC. Three hypotheses will be tested: (1) overweight troops are being accurately detected by the current methods of weight and fat evaluation; (2) overweight troops are successfully losing weight; and (3) overweight troops who achieve their weight standard and are deleted from the program are successfully maintaining the standard.

#### METHOD

Three study groups will be followed for 12 months: an infantry unit, a support unit, and MAMC. These are estimated to contain a total of 300-400 overweight troops. The three different types of units have been selected for comparison in order to determine if the consistency of the application of the regulation and the distribution of individuals with weight disorders are related to unit mission.

Following a regular weigh-in, cooperating units will be asked to submit weigh-in lists with weight, height, age, sex, rank, and overweight program status for every individual obtainable. This will provide the information on percent of troops currently overweight. Body fat assessments on these individuals will be submitted to the Nutrition Clinic. Individuals who are overweight at the first weigh-in will be followed by weigh-ins at subsequent intervals of 6 and 12 months. If possible, information on individual methods of weight loss will also be obtained.

Initial body weights and subsequent 6 and 12 month weights will be used to determine the proportions who: are on schedule with their weight goals but which have not yet achieved the standard at six months; achieve their weight goals and are deleted from the program; achieve their weight goals, are deleted from the program, and are again overweight; have been lost from observation due to transfer or other administrative action; and were not picked up on the weight program even though they are overweight.

Assessment of the Impact of the Weight Program at Fort Lewis and  
MAMC - Dewinne

PROGRESS

Data entry and analysis are being finalized and a manuscript is in preparation. Preliminary analysis indicate that over half of the individuals entered in the weight program between May 1983 and August 1984 met weight loss goals (40%) or made satisfactory progress toward those goals (15%) in the first six months on the program. This group demonstrated an average weight loss of three pounds per month. A smaller subset achieved their goals and promptly regained weight. Less than 20% left active duty through retirement, ETS, or administrative action. Twenty percent of individuals were continued on the program beyond six months, without demonstrating satisfactory progress. Seven percent of the sample were lost from records due to PCS or for unexplained reasons.

Preliminary review of skinfold data indicates differences in certain ethnic, age, and sex subpopulations for proportions of people who exceeded the height-weight tables but were below their accepted standard of fatness. Previously reported demographic differences in specific skinfold sites are here confirmed for an exclusively overweight population.

The inter- and intra-rater reliabilities of certified Ft Lewis caliper users is still being assessed with attention to variation in individual measurement sites.

STATSU: (O)

TITLE: FHCRC #11 - Protocol for Treatment of Adult Acute  
Nonlymphocytic Leukemia, Study V.

PRINCIPAL INVESTIGATOR: LTC Irwin B. Dabe, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC James E. Congdon, MC  
MAJ Thomas M. Baker, MC  
MAJ Alfred H. Chan, MC  
MAJ Howard Davidson, MC  
MAJ Timothy J. O'Rourke, MC

WORK UNIT NO: 83/30

#### TECHNICAL OBJECTIVES

To determine the complete remission rate with intensive induction in patients with ANL; to determine if therapy with high-dose Ara-C, Asparaginase, AMSA, and VP-16 will decrease the rate of leukemic relapse; to determine whether the wider application of marrow transplantation using allogeneic, partially-matched, unrelated, and autologous marrow will increase the cure rate of ANL in patients less than 30 years of age; and to determine if marrow transplantation should be carried out in first remission or at first sign of relapse in patients age 30-50.

#### METHOD

All Patients <75 years with adult nonlymphocytic leukemia, previously untreated except for the administration of hydroxyurea are eligible. Diagnoses to be included: acute myelocytic, promyelocytic, monocytic, myelomonocytic, acute undifferentiated, and erythroleukemic. Daunomycin, Ara-C, 6-thioguanine, vincristine, and prednisone will be used in Cycle I as the induction regimen; Cycle 2 will be high-dose Ara-C and asparaginase; Cycle III - same as Cycle I; Cycle IV will be high dose AMSA and VP-16; cycle V - same as Cycle I, Cycle VI will be vincristine, prednisone, 6-mercaptopurine, and methotrexate. Regardless of remission status, patients <30 will be offered bone marrow transplantation after Cycle 2. Patients 30-50 years of age who have not achieved complete remission after two courses or who relapse after remission will be offered transplantation. Patients >50 will receive chemotherapy only. All patients will continue on chemotherapy, regardless of transplantation status.

#### PROGRESS

One patient entered in FY 84. The patient had fairly severe side effects to the chemotherapy with multiple admissions for infection and leukopenia.

STATUS: (O)

D E T A I L   S H E E T S  
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FRED HUTCHINSON CANCER RESEARCH CENTER GROUP PROTOCOLS



**TITLE:** CCG #861: Surgery, Radiation Therapy, and Chemotherapy with Bleomycin, Vinblastine, Cis-Platinum Diamine Dichloride, Actinomycin-D, Cyclophosphamide, and Adriamycin in the Treatment of Local and Metastatic Malignant Germ Cell Ovarian Tumors of Childhood (Phase II Study)

**PRINCIPAL INVESTIGATOR:** MAJ Allen R. Potter, MC

**PROFESSIONAL ASSISTANTS:** LTC Charlene Holt, MC  
LTC Alan Mease, MC

**WORK UNIT NO:** 79/46

#### TECHNICAL OBJECTIVES

To determine, in patients with germ cell ovarian malignancy which has been completely excised by surgery, treated with 6-drug chemotherapy, and perhaps with radiation therapy, the length of disease free interval and the percentage of patients having long term survival; to determine, in patients with residual or metastatic disease treated with surgery, 6-drug chemotherapy, and radiation therapy, the effectiveness of the treatment program as indicated by percent of patients experiencing CR or PR and the length of the remission periods; to examine the relationship between age, tumor type, staging, and pathology with prognosis; and to determine if a single arm study of an infrequent childhood tumor is practical and produces significant conclusions.

#### METHOD

Patients will be treated with chemotherapy for 18 weeks. At week 18, a second look laparotomy is performed. If there is residual or persistent tumor present, radiation therapy will be given. If there is no residual or persistent tumor at this time, radiation therapy will not be administered. If at 24 weeks the patient has progressive disease, the patient will be taken off the study. Patients on the study will continue chemotherapy until week 102. The patient will be taken off the study if there is progressive disease after 24 weeks of therapy or if recurrent or metastatic disease appears after six months of therapy.

#### PROGRESS

No entries at MAMC.

**STATUS:** (O)

TITLE: CCG #251: Treatment of Newly Diagnosed Acute  
Non-Lymphocytic Leukemia with Multiagent Chemotherapy  
(Cyclic Versus Continuous) or Bone Marrow Transplantation  
Following Total Body Irradiation

PRINCIPAL INVESTIGATOR: MAJ Allen R. Potter, MC

PROFESSIONAL ASSISTANT: LTC Alan D. Mease, MC

WORK UNIT NO: 81/103

#### TECHNICAL OBJECTIVES

To improve remission duration and survival in children with previously untreated acute non-lymphocytic leukemia using Cytosan and total body irradiation followed by bone marrow transplantation with compatible donor marrow for those children who achieve a complete remission with induction therapy; to compare two intensive maintenance regimens; continuous 6-thioguanine with monthly courses of Cytosan, vincristine, 5-azacytidine, and cytosine arabinoside vs repeated cycles of 6-thioguanine and cytosine arabinoside; adriamycin and cytosine arabinoside; prednisolone, vincristine, methotrexate, and 6-mercaptopurine; 5-azacytidine and adriamycin; and BCNU and cyclophosphamide; to evaluate the induction capabilities of adriamycin and cytosine arabinoside; and to evaluate the prognostic significance of any chromosomal abnormalities in leukemic cell lines.

#### METHOD

Induction therapy will consist of adriamycin and ARA-C given IV. When the bone marrow by aspiration is M-1 (day 29) or M-2 (day 57), subjects will receive one of the two intensive maintenance regimens listed above with concomitant radiotherapy or bone marrow transplant preceded by two successive days of Cytosan therapy, followed four days later by total body irradiation. Patients 21 years of age at diagnosis who have previously untreated acute non-lymphocytic leukemia will be eligible.

#### PROGRESS

(7/81 - 9/84) One patient was entered at MAMC with good results. No patients currently on protocol.

STATUS: (C)

**TITLE:** CCG 191P - Total Sanctuary vs Conventional CNS Treatment of Newly Diagnosed Acute Lymphoblastic Leukemia for Patients with "Average Risk" and "High Risk" Prognostic Characteristics, Phase III

**PRINCIPAL INVESTIGATOR:** MAJ Allen R. Potter, MC

**PROFESSIONAL ASSISTANTS:** LTC Charlene P. Holt, MC  
LTC Alan D. Mease, MC

**WORK UNIT NO:** 79/89

#### TECHNICAL OBJECTIVES

To compare the effects of high-dose, protracted IV methotrexate infusion vs standard cranial irradiation plus IT methotrexate on: (1) central nervous system relapse; (2) central nervous system toxicity - both acute and delayed; (3) hematologic remission induction and duration; (4) non-CNS extramedullary relapse (e.g. testes); and (5) survival.

#### METHOD

Previously untreated patients <21 years of age with acute lymphoblastic leukemia who are <3 years old, >7 or have have an initial WBC of greater than 10,000/ $\mu$ l will be eligible. patients with the diagnosis of acute undifferentiated leukemia on any initial WBC will be treated on this protocol but analyzed as a separate group. Patients will be treated initially with prednisone, vincristine, L-asparaginase, daunomycin, and central nervous system prophylaxis. The type of CNS prophylaxis will be determined by randomization and will consist either of very high doses of methotrexate IV or cranial radiation plus IT methotrexate. Most of the CNS therapy will be given during the second month of treatment, during which 6-MP will replace the daunomycin and L-asparaginase. From the third month on, remission will be maintained by a sequence of multiple drug administrations, including vincristine, prednisone, L-asparaginase, daunomycin, methotrexate, cyclophosphamide, and 6-MP. M<sub>3</sub> bone marrow or extramedullary leukemia at any time will be cause for removal from the study.

#### PROGRESS

(7/79 - 9/84) The total sanctuary arm proved to be definitely superior as far as decreasing bone marrow relapses in average risk patients. CNS relapse rate appears to be not significantly different between the two groups.

No new patients were entered at MAMC in FY 84 and there are none still on the protocol so it has been closed.

**STATUS:** (C)

D E T A I L   S H E E T S  
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CHILDRENS CANCER STUDY GROUP PROTOCOLS

**TITLE:** Efficacy of Diphenylhydantoin in the Prevention of Acute Mountain Sickness

**PRINCIPAL INVESTIGATOR:** MAJ Lawrence C. Mohr, MC

**PROFESSIONAL ASSISTANTS:** COL William N. Bernhard, MC (USAR)  
COL Stephen R. Plymate, MC  
CPT Karl E. Friedl, MSC  
CPT Jerome Pierson, MSC  
Allan Cymerman, Ph.D., USARIEM

**WORK UNIT NO:** 84/76

#### TECHNICAL OBJECTIVES

To determine the efficacy of diphenylhydantoin (Dilantin) in a dosage of 200 mg 2 times daily after a 600 mg loading dose in preventing acute mountain sickness in soldiers making a rapid ascent of Mount Rainier and to determine the effect of Dilantin on the performance of soldiers during the rapid ascent.

#### METHOD

Subjects will be selected on the basis of fitness, motivation and mountaineering aptitude. Subjects will be divided into two groups, matched closely for age, weight, fitness, and previous altitude experience. Subjects will be given either Dilantin or a placebo every 12 hours from 24 hours before ascent until descent. A loading dose will be given orally in 2 doses 6 hrs apart. Blood will be drawn before and after the climb for analysis.

The subjects will drive to the starting point (about 5400 feet), climb to between 10,000 and 11,500 feet, remain eight hours for repeat testing, and then proceed to 14,000 feet where they will remain for 1-2 hours of tests before descending. In a subsequent climb, the order of treatment groups will be reversed.

The ARIEM Environmental Symptoms Questionnaire (ESQ) will be administered before going to 5400 feet, at each stage of the ascent and after descent. Subjects will be tested by ESQ and performance tests over a similar duration of time without ascent to altitude with the same Dilantin regimen to distinguish interactions between Dilantin and altitude effects. Performance will be assessed with the finger tapping speed test and the paced serial addition test at the various stages of the experiment. Physiological measurements will be made for each subject at the same stages as the ESQ test to include corticosteroids, catecholamines, osmolarity, electrolytes, vital capacity, minute ventilation, peak expiratory flow rates, pulse, blood pressure, and degree of hypoxia.

#### PROGRESS

Pilot studies were done to achieve an optimal loading dose and to perfect the experimental sequence for a larger group. This study will be continued after June 1985.

**STATUS:** (O)

**TITLE:** High Dose Acetazolamide and Acute Mountain Sickness -  
Clinical Efficacy and Effect on Military Performance

**PRINCIPAL INVESTIGATOR:** MAJ Lawrence C. Mohr, MC

**PROFESSIONAL ASSISTANTS:** COL William N. Bernhard, MC (USAR)  
CPT Jerome Pierson, MSC

**WORK UNIT NO:** 84/63

#### TECHNICAL OBJECTIVES

To determine the efficacy of high dose acetazolamide in preventing acute mountain sickness in soldiers making a rapid ascent of Mount Rainier and to determine the effect of high dose acetazolamide the performance of soldiers during a rapid ascent of Mount Rainier.

#### METHOD

Approximately 30 soliders who are making a rapid ascent of Mount Rainier as part of their training will be recruited for this study. Subjects will have a complete medical history, review of systems and physical examination performed prior to the ascent. Soldiers will be excluded from the study if they have evidence of heart or pulmonary disease, or renal, hepatic, or adrenal dysfunction. Venous blood samples will be drawn prior to ascent and after ascent and at the summit to determine serum electrolyte, bicarbonate, glucose, osmolality, cortisol, endorphin, testosterone and lactate. Saliva samples for cortisol and testosterone will also be collected. Soldiers will eat a standard diet of C-Rations or MRE-Rations three times/day during the ascent and water intake and urine output will be recorded.

Subjects will be assigned to receive acetazolamide (Diamox) or a placebo, every 12 hours beginning 24 hours prior to ascent. A standard Environmental Symptoms Questionnaire will be completed at the summit and immediately before and after the climb. Performance will be assessed by having each subject connect the dots of a standard Bender pattern and copy a standard Bender solid-line figure before and after the climb and at the summit. The following measurements will be made in each subject at each altitude at which the subjects complete the Environment Symptoms Questionnaire: pulse rate; blood pressure; tissue  $pO_2$ ; vital capacity; minute ventilation; and peak expiratory flow. Data from the acetazolamide and placebo groups will be evaluated with paired and unpaired Student's t test, chi square test with Yate's continuity correction, or Fisher's exact test.

#### PROGRESS

A pilot study was performed, but poor weather conditions made it impossible to achieve the desired altitude for the acetazolamide test. This study will be continued in June 1985. This initial study yielded endocrine findings which have been accepted for presentation at the Third International Congress of Andrology.

**STATUS:** (O)

TITLE: Ranger Medic Procedures Training

PRINCIPAL INVESTIGATOR: CPT Robert E. Kane, MC

PROFESSIONAL ASSISTANT: MAJ Stanley P. Liebenberg, VC

WORK UNIT NO: 83/34

#### TECHNICAL OBJECTIVE

To provide training to acquire the necessary manipulative skills in performing emergency life-saving measures in support of wartime field operations.

#### METHOD

The Medical Platoon of the 2/75th Infantry (Ranger) consists of two MC officers and approximately 20 additional enlisted personnel (MOS 91B). Each of these 20 personnel will be trained on a quarterly basis. Classes will be conducted monthly utilizing the two MC officers as preceptors, training 6-7 Ranger medics at each session.

Two mongrel dogs will be used for each training class with the exception of debridement exercises which will each use four sheep as animal models. All animals will initially be anesthetized with sodium pentobarbital with anesthesia maintained by halothane throughout the duration of each class. Wounds for debridement will be caused by a Captive Bolt Pistol. Upon completion of the exercise, all animals will be euthanized by lethal injection of sodium pentobarbital without allowing the animal to regain consciousness. The carcasses will be disposed of by incineration. Procedures to be performed on dogs consist of:

|   |                     |
|---|---------------------|
| Peripheral venous cutdown (femoral/jugular) | Pericardiocentesis  |
| Tube thoracotomy (chest tube insertion)     | Peritoneal lavage   |
| Resuscitative techniques                    | Suturing techniques |
| Reversal of hypovolemic shock               | Cricothyroidotomy   |

#### PROGRESS

This protocol was active during the first part of the year with several training sessions. However, because of the moratorium on the use of dogs in clinical research initiated by DoD, this project is currently suspended.

STATUS: Suspended

D E T A I L   S H E E T S  
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9TH INFANTRY DIVISION



TITLE: An Explanatory Study of the Exceptional Family Member Program

PRINCIPAL INVESTIGATOR: MAJ Robert H. Gemmill, MSC

PROFESSIONAL ASSISTANTS: LTC Virginia Randall, MC

WORK UNIT NO: 84/53

#### TECHNICAL OBJECTIVES

To describe characteristics of the exceptional family member population and to study how Army active duty personnel with exceptional family members perceive the Exceptional Family Member Program.

#### METHOD

This protocol will also be conducted at BAMC and WBAMC.

A questionnaire will be distributed to all adult soldiers who voluntarily come to the Pediatric Clinic to initiate processing for The Exceptional Family Member Program. The questionnaire will also be distributed to those soldiers who are eligible to participate in the program, but who have not yet enrolled.

The questions to be explored are: What are the characteristics of the exceptional family member population; how much accurate knowledge is there about the program? how well is the program being accepted; how can the program be improved or made more productive; what are the strengths and weaknesses of the program; and how accurate are the goals of the program being perceived by the recipients of the program.

#### PROGRESS

The first three chapters (The Problem, Review of Literature, and Methodology) of the dissertation have been completed. Due to a lower than expected questionnaire return rate, questionnaire distribution will continue until the end of October 1984. Analysis of the data will be conducted in November 1984 and Chapters IV and V will be completed by January or early February 1985. The oral defense of the dissertation is planned for March 1985, after which the final format is to be completed.

STATUS: (O)

D E T A I L   S H E E T S

F O R

P R O T O C O L S

A C T I V E D U T Y F U L L T I M E S T U D E N T S

**TITLE:** Hepatitis B Screening Program in Obstetrics and Sexually Transmitted Disease Clinics Populations at a Large Military Post

**PRINCIPAL INVESTIGATOR:** MAJ Duong Nguyen, MC

**PROFESSIONAL ASSISTANTS:** COL John Read, MC  
LTC Carl Stones, MC  
CPT David Fletcher, MC  
Thomas Koepsell, M.D., Univ of Washington

**WORK UNIT NO:** 84/21

#### TECHNICAL OBJECTIVES

To define the high risk group for Hepatitis B in the military obstetric clinic population and in the sexually transmitted diseases clinic populations.

#### METHOD

A questionnaire will be given to all prenatal first visit OB patients at MAMC and the Special Adult Clinic (STD Clinic) to collect demographic data as well as symptoms and exposure history to hepatitis. OB patients will have a HBsAg test blood sample drawn at the same time as the prenatal test package workup. STD Clinic patients will have HBsAg blood drawn with the routine RPR test. Patients with a positive HBsAg test will have a repeat test with more specific antisera for confirmation purposes and an HBeAg test. Patients will be referred to Internal Medicine or to Chief, OB Service for further management.

Data will be examined in terms of frequency distributions and significance will be analyzed by nonparametric tests of differences between proportions at the  $p < 0.01$  significance level.

#### PROGRESS

(12/83 - 9/84) HBsAg was detected in 1.8% of 1292 patients studied from the STD clinic and in 0.5% of 1135 patients studied from the OB prenatal clinic. From the STD clinic, the high risk group is defined as a black male, in his twenties, with a high school education, and having been overseas. All the six positive cases from the OB clinic were from minority groups. The investigators recommend that a routine HBsAg screening test be performed in all STD clinic patients and all high-risk OB patients and hepatitis B immune globulin and HB Vac should be given to eligible candidates.

**STATUS:** (C)

D E T A I L   S H E E T S  
F O R  
P R O T O C O L S

P R E V E N T I V E   M E D I C I N E   S E R V I C E

TITLE: FHCRC 102 - Protocol for the Treatment of Adult Acute Lymphoblastic Leukemia (ALL)

PRINCIPAL INVESTIGATOR: LTC Irwin B. Dabe, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC James E. Congdon, MC  
MAJ Thomas M. Baker, MC  
MAJ Alfred H. Chan, MC  
MAJ Howard Davidson, MC  
MAJ Timothy J. O'Rourke, MC

WORK UNIT NO: 83/53

#### TECHNICAL OBJECTIVES

To determine the complete remission rate with intensive induction in adults with ALL; to determine the overall survival of patients treated with this intensive consolidation and maintenance therapy; and to determine the remission duration and overall survival of patients treated with CY and TBI and a HLA matched sibling bone marrow transplant while in first remission and to compare the results with those patients who achieve a remission and are continued on chemotherapy.

#### METHOD

All patients with acute lymphoblastic leukemia over the age of 18 and less than age 50 who are previously untreated except for the administration of hydroxyurea, prednisone, and vincristine are eligible. Also included will be young adults with lymphoblastic lymphoma (T cell variant). Individuals will be treated with one or two cycles of a four-drug regimen. Those not achieving a remission after two cycles of induction therapy will be taken off study and treated with other drugs. Those who have a tissue match with a donor will be followed by no further leukemic treatment unless they relapse. Those without a tissue match will be treated with further drug treatment for 15 ten-week cycles at which time therapy will be stopped and they will be followed closely. Spinal taps and bone marrow exams will be done periodically during consolidation and maintenance drug therapy.

#### PROGRESS

(3/83 - 9/84) No patients have been entered. This protocol was terminated groupwide due to the extremely slow accrual rate of subjects.

STATUS: (T)

TITLE: FHCRC #143: Treatment of Relapsed Acute Nonlymphocytic Leukemia with AMSA, and Use of in Vitro Studies (Stem Cell Assay) to Predict a Response in Vivo.

PRINCIPAL INVESTIGATOR: LTC Irwin B. Dabe, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC James E. Congdon, MC  
MAJ Thomas M. Baker, MC  
MAJ Alfred H. Chan, MC  
MAJ Howard Davidson, MC  
MAJ Timothy J. O'Rourke, MC

WORK UNIT NO: 83/48

#### TECHNICAL OBJECTIVE

To determine the ability of AMSA to induce remission for patients with acute nonlymphoblastic leukemia in relapse.

#### METHOD

Patients who have relapsed after successful induction of remission with daunomycin and cytosine arabinoside, as well as patients who have failed two cycles of remission induction therapy, are eligible for this study. The factors that will be analyzed include duration of first remission, nature and amount of previous chemotherapy received, age and number of cycles of therapy to first complete remission. Patients will receive AMSA 120 mg/M<sup>2</sup> for five days. A bone marrow exam will be done on day 14. If the marrow has more than 30% blasts when the marrow is hypocellular or more than 10% when the marrow is normocellular, a second induction course will be given. A minimum of two courses is needed to evaluate response. If after two courses a complete remission is not reached and the patient has not had undue toxicity, a third course may be given.

#### PROGRESS

One patient entered at MAMC in FY 84 with a partial response only. AMSA remains one of the few agents with activity in AML relapsed patients after prior treatment, but overall groupwide response rate is low with severe cytopenia and short duration of response.

STATUS: (O)

TITLE: FHCRC #152: Combined Modality Treatment for Non-Hodgkin's Lymphomas of Intermediate and High-Grade Malignancy

PRINCIPAL INVESTIGATOR: MAJ Howard Davidson, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC James E. Congdon, MC  
LTC Irwin B. Dabe, MC  
MAJ Thomas M. Baker, MC  
MAJ Alfred H. Chan, MC  
MAJ Timothy J. O'Rourke, MC

WORK UNIT NO: 83/47

#### TECHNICAL OBJECTIVE

To compare in patients with extensive (stage III and IV), aggressive (intermediate and high-grade malignancy) non-Hodgkin's lymphoma (NHL) the response rate, duration, and survival after treatment with: (1) combined cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP) chemotherapy combined with total body irradiation (TBI), or (2) CHOP chemotherapy combined with upper and lower hemibody irradiation (HBI); and to determine the response rate, duration and survival of patients with limited (stage I, II, and certain stage III and IV), aggressive NHL treated with CHOP chemotherapy with local radiotherapy.

#### METHOD

After appropriate tests to determine the extent of the lymphomas, patients will receive 4 cycles of multi-agent chemotherapy to include cytoxan, adriamycin, oncovin and prednisone. At the end of 4 cycles of chemotherapy, given 4 weeks apart, patients will be restaged to determine the extent of remaining disease. If there is at least a 50% reduction in the observed disease, the patients will proceed to Phase II consisting of radiation therapy. All patients will receive prednisone every other day by mouth and vincristine IV every other week. Those patients with disease involving <50% of the body will receive limited radiation therapy to sites of known lymphoma involvement. Those patients with extensive disease will be randomized to receive either low dose total body radiation or low dose sequential hemibody radiation therapy. At the completion of Phase II, all patients will receive 4 more cycles of CHOP with the intervals lengthened to 8 weeks. At the end of Phase III, if there is no evidence of remaining disease, patients will be taken off therapy and observed.

#### PROGRESS

Two patients were entered at MAMC in FY 84 for a total of five subjects. Of the five patients entered, one (Stage I) continues to be followed in complete remission, three were in remission when lost to follow-up, and one died of recurrent disease.

STATUS: (O)

D E T A I L   S H E E T S

F O R

P R O T O C O L S

GYNECOLOGY ONCOLOGY GROUP PROTOCOLS



TITLE: GOG #26C: A Phase II Trial of Cis-Platinum Diamminedichloride

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANTS: COL William L. Benson, MC

WORK UNIT NO: 82/07

#### TECHNICAL OBJECTIVE

To determine the efficacy of cis-platinum diamminedichloride in patients whose advanced malignancies have been resistant to higher priority methods of treatment.

#### METHOD

All patients with measurable gynecological cancer, who have failed higher priority therapies, will be offered cis-platinum as a Phase II drug to determine its efficacy. The drug is given at 50 mg/M<sup>2</sup> intravenously every three weeks as toxicity permits. Patients who respond or who demonstrate disease will continue to receive the agent until progression has occurred.

#### PROGRESS

One patient entered on this protocol during FY 84; given seven courses of Cis-platinum with no response.

STATUS: (0)

TITLE: GOG #26D: A Phase II Trial of VP-16 in Patients with  
Advanced Pelvic Malignancies

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 83/18

#### TECHNICAL OBJECTIVE

To determine the efficacy of VP-16 in patients whose advanced malignancies have been resistant to higher priority methods of treatment.

#### METHOD

All patients with measurable gynecological cancer who have failed higher prior therapies will be offered VP 16 as a Phase II drug to determine its efficacy. The drug will be given as 100 mg/M<sup>2</sup> intravenously on days 1, 3, and 5, every four weeks. Patients who respond or demonstrate disease will continue to receive the agent until progression has occurred.

#### PROGRESS

No patients entered at MAMC.

STATUS: (0)

TITLE: GOG #26E: A Phase II Trial of Glactitol 1,2:5,6-Dianhydro  
in Patients with Advanced Pelvic Malignancies

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANTS: COL William L. Benson, MC

WORK UNIT NO: 83/19

#### TECHNICAL OBJECTIVE

To determine the efficacy of glactitol 1,2:5,6-dianhydro in patients whose advanced malignancies have been resistant to higher priority methods of treatment.

#### METHOD

All patients with measurable gynecological cancer who have failed higher prior therapies will be offered glactitol 1,2:5,6-dianhydro as a Phase II drug to determine its efficacy. The drug will be given as 60 mg/M<sup>2</sup> slow I.V. push weekly. If no toxicity has occurred after 4 doses, the dosage will be increased to 75 mg/M<sup>2</sup> weekly. Patients will continue to receive the agent until progression occurs.

#### PROGRESS

No patients entered at MAMC.

STATUS: (O)

TITLE: GOG #26G: A Phase II Trial of ICRF-159 in Patients with  
Advanced Pelvic Malignancies

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 83/20

#### TECHNICAL OBJECTIVE

To determine the efficacy of ICRF-159 in patients whose advanced malignancies have been resistant to higher priority methods of treatment.

#### METHOD

All patients with measurable gynecological cancer who have failed higher prior therapies will be offered ICRF-159 as a Phase II drug to determine its efficacy. The drug will be given by mouth as 1.5 gm/M<sup>2</sup>, in three divided doses, one every 6 hours, on day 1, repeated weekly as marrow recovery permits. Patients will continue to receive the agent until progression occurs.

#### PROGRESS

One patient was entered in FY 83, exhibited no response to ICRF, and died from disease in FY 84.

STATUS: (0)

TITLE: GOG #26I: A Phase II Trial of AMSA in Patients with Advanced  
Pelvic Malignancies

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 83/21

#### TECHNICAL OBJECTIVE

To determine the efficacy of AMSA in patients whose advanced malignancies have been resistant to higher priority methods of treatment.

#### METHOD

All patients with measurable gynecological cancer who have failed higher prior therapies will be offered AMSA as a Phase II drug to to determine its efficacy. The drug will be given as 60 mg/M<sup>2</sup> I.V. once every 28 days. Patients will continue to receive the agent until progression occurs.

#### PROGRESS

No patients entered at MAMC.

STATUS: (O)

TITLE: GOG #26J: A Phase II Trial of Yoshi 864 in Patients with  
Advanced Pelvic Malignancies

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 83/22

TECHNICAL OBJECTIVE

To determine the efficacy of Yoshi 864 in patients whose advanced malignancies have been resistant to higher priority methods of treatment.

METHOD

All patients with measurable gynecological cancer who have failed higher prior therapies will be offered Yoshi 864 as a Phase II drug to determine its efficacy. The drug will be given as 1.5 mg/kg/d x 5 I.V. every six weeks. Patients will continue to receive the agent until progression occurs.

PROGRESS

No patients entered at MAMC.

STATUS: (0)

TITLE: GOG #26L (Part 2): A Phase II Trial of Tamoxifen  
(NSC 180793) in Patients with Advanced Epithelial Ovarian  
Carcinoma, Part II

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANTS: COL William Benson, MC

WORK UNIT NO: 83/52

#### TECHNICAL OBJECTIVE

To determine the efficacy of tamoxifen in patients whose advanced malignancies have been resistant to higher priority methods of treatment.

#### METHOD

All patients with measurable gynecological cancer who have failed higher prior therapies will be offered tamoxifen as a Phase II drug to determine its efficacy. The drug will be given as 20 mg PO b.i.d. until adverse effects prohibit further therapy. A minimum trial will be defined as receiving a minimum of eight weeks of therapy.

#### PROGRESS

No patients entered at MAMC.

STATUS: (O)

TITLE: GOG #26M: A Phase II Trial of PALA in Patients with Advanced  
Pelvic Malignancies

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 83/23

#### TECHNICAL OBJECTIVE

To determine the efficacy of PALA in patients whose advanced malignancies have been resistant to higher priority methods of treatment.

#### METHOD

All patients with measurable gynecological cancer who have failed higher prior therapies will be offered PALA as a Phase II drug to determine its efficacy. The drug will be given as 5.0 mg/M<sup>2</sup> I.V. every three weeks. Patients will continue to receive the agent until progression or adverse effects prohibit further therapy.

#### PROGRESS

No patients entered at MAMC.

STATUS: (0)



TITLE: GOG #26N: A Phase II Trial of Dihydroxyanthracenedione (DHAD) in Patients with Advanced Pelvic Malignancies

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 83/24

#### TECHNICAL OBJECTIVE

To determine the efficacy of DHAD in patients whose advanced malignancies have been resistant to higher priority methods of treatment.

#### METHOD

All patients with measurable gynecological cancer who have failed higher prior therapies will be offered DHAD as a Phase II drug to to determine its efficacy. The drug will be given as 12 mg/M<sup>2</sup> I.V. every three weeks. Patients will continue to receive the agent until progression or adverse effects prohibit further therapy.

#### PROGRESS

One patient was entered in FY 83 with progression of disease and death in FY 84.

STATUS: (O)

TITLE: GOG #26-O: A Phase II Trial of Aziridinybenzoquinone  
(AZQ) in Patients with Advanced Malignancies

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANTS: COL William L. Benson, MC

WORK UNIT NO: 82/30

#### TECHNICAL OBJECTIVE

To determine the efficacy of AZQ in patients whose advanced malignancies have been resistant to high priority methods of treatment.

#### METHOD

All patients with measurable gynecological cancer who have failed higher prior therapies will be offered AZQ as a Phase II drug to determine its efficacy. The drug will be given as 30 mg/M<sup>2</sup> given every three weeks. Patients will continue to receive the agent until progression or adverse effects prohibit further therapy.

#### PROGRESS

One patient entered at MAMC during FY 84 with no response to AZQ; death by cancer of cervix.

STATUS: (0)

TITLE: GOG #48: A Study of Progestin Therapy and a Randomized Comparison of Adriamycin vs Adriamycin Plus Cyclophosphamide in Patients with Advanced Endometrial Carcinoma After Hormonal Failure (Phase III Study)

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 81/43

#### TECHNICAL OBJECTIVES

To evaluate the response of advanced or recurrent endometrial carcinoma to oral progestins in patients who have received no prior hormonal therapy for cancer; and to compare a combination of adriamycin and cyclophosphamide to adriamycin alone as therapy for advanced or recurrent endometrial carcinoma which no longer responds to or has failed to respond to progestins in patients who have received no prior cytotoxic drugs.

#### METHOD

Patients with documented primary Stage III, Primary Stage IV, recurrent or residual endometrial adenocarcinoma, adenoacanthoma, or adenosquamous carcinoma, whose potential for cure by radiation therapy or surgery alone or in combination is very poor, are eligible for this study. Patients who have received previous chemotherapy are ineligible. Patients will be randomized.

Regimen 1: adriamycin 60 mg/M<sup>2</sup> IV q 3 weeks x 8 courses. Responders will have follow-up only. Those with progression will be transferred to Protocol #26.

Regimen 2: adriamycin 60 mg/M<sup>2</sup> IV q 3 weeks x 8 courses plus cyclophosphamide 500 mg/M<sup>2</sup> IV q 3 weeks x 8 courses. Responders will receive follow-up only. Those with progression will be transferred to Protocol #26. Those patients with no prior hormonal therapy will be placed on C.T. Provera for a minimum of 12 weeks. Those with progression of disease at any time after 12 weeks will be randomized as above.

#### PROGRESS

One patient entered in FY 84, for a total of three subjects. One patient died from cancer, one patient has progression of disease, and one is free of disease.

STATUS: (O)

TITLE: GOG 45: Evaluation of Vinblastine, Bleomycin, and  
Cis-Platinum in Stages III and IV and Recurrent Malignant  
Germ Cell Tumors of the Ovary

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANTS: COL William L. Benson, MC

WORK UNIT NO: 84/46

#### TECHNICAL OBJECTIVES

To evaluate the effect of four cycles of combined vinblastine, bleomycin and cis-platinum (VBP) chemotherapy in the management of patients with endodermal sinus tumor, embryonal carcinoma, immature teratoma (all grades), choriocarcinoma, and malignant mixed germ cell tumors of the ovary with advanced or recurrent disease, incompletely resected; to evaluate the role of serum markers, especially alphafetoprotein and human chorionic gonadotropin when these are present in predicting response and relapse; to determine the role of restaging laparotomy in patients in clinical remission in assessing completeness of response and in planning further therapy; to evaluate and compare the effect of vincristine, dactinomycin, and cyclophosphamide (VAC) chemotherapy in patients found to have persistent disease at the time of restaging laparotomy.

#### METHOD

Patients with advanced or recurrent germ cell tumors of the ovary are eligible for this protocol using VBP. Those patients who respond to chemotherapy will have re-exploratory laparotomy. All patients determined to have a surgical complete response will be followed without any further therapy. Those patients who still have cancer or who progressed under VBP will be treated with VAC.

#### PROGRESS

No patients entered at MAMC.

STATUS: (0)

TITLE: GOG #44: Evaluation of Adjuvant Vincristine, Dactinomycin, and Cyclophosphamide Therapy in Malignant Germ Cell Tumors of the Ovary After Resection of all Gross Tumor, Phase III

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 81/25

#### TECHNICAL OBJECTIVES

To evaluate the effect of combined prophylactic vincristine, dactinomycin, and cyclophosphamide (VAC) chemotherapy in patients with endodermal sinus tumor, embryonal carcinoma, immature teratoma (Grades 2 and 3), choriocarcinoma, and malignant mixed germ cell tumors of the ovary, Stages I and II, after total removal of all gross tumor; to evaluate the role of serum markers, especially alpha-feto-protein and human chorionic gonadotropin (beta HCG), when these are present in predicting response and relapse; to determine the role of restaging laparotomy in determining response, predicting relapse, and planning further therapy.

#### METHOD

Patients with histologically confirmed malignant germ cell tumors of the ovary, Stage I or II, if previously untreated and completely resected, (excluding patients with pure dysgerminoma) will be eligible. Patients with Grade 2 or 3 immature teratoma are eligible. After adequate recovery from required surgery, patients will receive 6 courses of VAC chemotherapy. If progression is noted during chemotherapy, patients will be transferred to the appropriate protocol. Patients with no evidence of disease after 6 courses will then undergo a restaging laparotomy. Those showing evidence of progression will be transferred. If laparotomy reveals no evidence of disease, patients will receive an additional 3 courses of VAC and then be followed on no further therapy.

#### PROGRESS

Two patients entered at MAMC during FY 84. Both patients completed the VAC chemotherapy. They are alive without evidence of disease.

STATUS: (0)

TITLE: GOG #41: Surgical Staging of Ovarian Carcinoma

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 81/35

#### TECHNICAL OBJECTIVES

To determine the spread of ovarian carcinoma to intraperitoneal structures and retroperitoneal lymph nodes by direct examination, cytologic sampling, and biopsy; to establish a surgical protocol for patients entered into GOG ovarian cancer treatment protocols; to determine the complication rate of the procedures.

#### METHOD

There will be no change in the surgical procedures performed. This protocol is being performed as a statistical protocol. These will be patients who have surgery as standard treatment. Eligible patients will be those who have Stages I, II, or III (optimal) ovarian carcinoma. Patients undergoing total abdominal hysterectomy, bilateral or unilateral salpingo-oophorectomy, bivalving of the other ovary, selective pelvic and para-aortic lymphadenectomy, omental biopsy, or peritoneal cytology sampling will be studied. They will not be given any preoperative treatment, but will be subjected to a complete and thorough evaluation before surgery. All patients will be explored and the steps for surgery will be as standard surgery dictates. Specific observations will be made as to the findings. If fluid is not present, washings will be taken from the inside of the abdomen to study cells. A thorough examination of all structures from the diaphragm to the pelvic floor will be carried out. After surgical staging, patients will be transferred to the appropriate treatment protocol or further treatment will be at the discretion of the investigator if no protocol is available.

#### PROGRESS

(1/81 - 9/84) One new patient was entered during FY 84. A total of 13 patients was entered at MAMC; two have expired from cancer and 11 are alive without evidence of disease.

The national group is preparing a paper for publication.

STATUS: (C)

TITLE: GOG #40: A Clinical-Pathologic Study of Stages I and II  
Uterine Sarcomas

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 81/79

#### TECHNICAL OBJECTIVES

The purpose of this study is to determine the incidence of pelvic and aortic lymph node metastases associated with Stages I and II uterine sarcomas, the relationship of these node metastases to other important prognostic factors such as mitotic index of the tumor, and the complication rate of the procedures. These findings will then be used as a guide for treatment protocols.

#### METHOD

Patients with histologically proven uterine sarcoma clinical Stages I or II who undergo total abdominal hysterectomy, bilateral salpingo-oophorectomy, selective pelvic and para-aortic lymphadenectomy, peritoneal cytology sampling and omentectomy (optional) as described in the protocol are eligible. Patients who have had prior preoperative adjuvant pelvic radiation or chemotherapy will be ineligible. The following pathologic evaluation will be done:

- a. Peritoneal cytology will be evaluated for malignant cells.
- b. The uterus will be evaluated at least in regard to:
  - (1) location of tumor; (2) depth of myometrial invasion;
  - (3) differentiation of tumor; (4) size of uterus;
  - (5) number of mitoses per 10 HPF; (6) histologic type of tumor.
- c. The adnexa will be evaluated for presence of metastasis.
- d. The lymph nodes will be evaluated as to metastasis and:
  - (1) location of involved lymph nodes and (2) number involved.

After surgical staging, patients may be transferred to an appropriate treatment protocol if all criteria are met. If no protocol is available, further treatment will be at the discretion of the physician.

#### PROGRESS

One patient entered at MAMC during FY 84, for a total of four subjects. One patient died from sarcoma, one has no evidence of disease, and two are alive with disease.

STATUS: (O)

TITLE: GOG #37: A Randomized Study of Radiation Therapy Versus  
Pelvic Node Resection for Patients with Invasive Squamous  
Cell Carcinoma of the Vulva Having Positive Groin Nodes

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 81/68

#### TECHNICAL OBJECTIVES

To determine the benefit and morbidity of adding adjunctive radiation therapy to pelvis and groin for patients found to have positive groin nodes at the time of radical vulvectomy and bilateral groin dissection.

#### METHOD

Eligible patients are those with primary previously untreated histologically confirmed invasive squamous cell carcinoma of the vulva, such that radical vulvectomy suffices to remove all of the local lesion, and whose surgery revealed that there were nodes in the groin on one or both sides containing metastatic carcinoma. Patients will be randomized to receive pelvic node dissection (the dissection will be carried out only on the side containing positive groin nodes or a bilateral if both sides are positive) or to receive bilateral groin and pelvic node irradiation. Major parameters to be studied are survival and time to recurrence. Patients will be followed quarterly for 3 years and every 6 months thereafter.

#### PROGRESS

No entries at MAMC. Group-wide, 112 patients were accrued and 90 patients were evaluable. The radiation therapy arm had superior progression-free interval and survival. The protocol is closed to further entry.

STATUS: (O)



TITLE: GOG #36: Surgical-Pathologic Study of Women with  
Squamous Cell Carcinoma of the Vulva

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 81/67

#### TECHNICAL OBJECTIVES

To determine by observations of 5-year survival and disease-free interval the validity of current FIGO staging to the histopathologic prognostic factors of size of lesion, location of lesion, depth of invasion of tumor in millimeters, histologic grade, and site and number of positive lymph nodes in Stages I-IV carcinoma of the vulva; to rapidly accumulate prospectively significant surgical pathologic data which would expedite development of further protocols for subsets of disease identified; to determine morbidity of primary radical surgical therapy.

#### METHOD

Eligible patients are those with primary, previously untreated histologically confirmed invasive squamous cell carcinoma of the vulva clinically determined to be Stage I through IV. Patients will be treated with radical vulvectomy plus bilateral groin dissection. The patients will undergo a thorough pelvic examination under anesthesia to assess pelvic structures and evaluate possible pelvic node disease. Those with negative groin nodes will be followed for 5 years without therapy. Those with positive groin nodes will be transferred to GOG #37. Relevant pathologic specimens will be studied.

#### PROGRESS

(3/81 - 9/84) No entries at MAMC. A paper is in preparation by the national group.

STATUS: (C)

TITLE: GOG #34: A Randomized Study of Adriamycin as an  
Adjuvant After Surgery and Radiation Therapy in Patients  
with HighRisk Endometrial Carcinoma Stage I and Occult  
Stage II

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 81/24

#### TECHNICAL OBJECTIVES

To study differences in morbidity and patient survival as  
functions of various tumor growth patterns as well as treatment  
in the high risk Stage I and, optionally, high risk Stage II  
occult endometrial carcinoma.

#### METHOD

Patients with primary, previously untreated, histologically  
confirmed invasive carcinoma of the endometrium, Stage I or II  
occult, all grades, with one or more of the following high risk  
criteria are eligible: (1) all lesions with equal to or greater  
than 1/2 myometrial involvement; (2) positive pelvic and/or para-  
aortic nodes; (3) microscopic evidence of cervical involvement  
but no gross clinical involvement of the cervix; (4) adnexal  
metastasis. Surgery will be followed in 2-6 weeks by "tailored"  
radiation therapy, pelvic and/or para-aortic, depending on node  
positivity. Prior to the initiation of radiation, therapy  
patients will be randomized to no further therapy or to adria-  
mycin beginning 2-4 weeks after radiation therapy.

#### PROGRESS

Four patients were entered during FY 84, for a total of eight  
subjects. All 8 are alive without recurrence.

STATUS: (0)

TITLE: GOG #33: A Clinical Pathologic Study of Stages I and II  
Carcinoma of the Endometrium

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 81/12

#### TECHNICAL OBJECTIVES

To determine the incidence of pelvic and aortic lymph node metastases associated with Stages I and II adenocarcinoma of the endometrium and the relationship of the node metastases to other important prognostic factors. These findings will then be used as a guide for treatment protocols.

#### METHOD

These patients will receive standard treatment; this protocol is only for data collection purposes. Patients with histologically proven endometrial carcinoma, clinical FIGO Stages I (grades 2 and 3) and Stage II (all grades) who have undergone total abdominal hysterectomy, bilateral salpingo-oophorectomy, selective pelvic and para-aortic lymphadenectomy, and peritoneal cytology sampling are eligible. The following histologic types of endometrial carcinoma are acceptable: adenocarcinoma, adenocarcinoma with squamous metaplasia, adenoacanthoma, and adenosquamous carcinoma. Patients who have received preoperative radiotherapy are ineligible. Pathologic evaluation will include:

- a. peritoneal washing will be evaluated for malignant cells;
- b. the uterus will be evaluated in regard to location of tumor, depth of myometrial invasion, differentiation of tumor, size of uterus;
- c. the adnexae will be evaluated for presence of metastasis;
- d. the lymph nodes (total number indicated) will be evaluated as to metastasis and location and number of lymph nodes involved.

After surgery, all patients will be entered into the appropriate protocol or receive appropriate treatment if no protocol is available.

#### PROGRESS

(12/80 - 9/84) Eight patients were entered on the protocol. Three of the eight patients had recurrence of endometrial cancer and died. A paper is in preparation by the national group.

STATUS: (C)

TITLE: GOG 26-T: A Phase II Trial of 4'-Deoxydoxorubicin in  
Patients with Advanced Pelvic Malignancies

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANTS: COL William L. Benson, MC

WORK UNIT NO: 84/65

#### TECHNICAL OBJECTIVE

To determine the efficacy of 4'-deoxydoxorubicin in patients whose advanced malignancies have been resistant to higher priority methods of treatment.

#### METHOD

All eligible patients who have failed higher priority therapies will be offered 4'-deoxydoxorubicin as a Phase II drug to determine its efficacy. The drug will be given at a dosage of 30 mg/M<sup>2</sup> every three weeks. Patients will be followed for toxicities to the drug and the drug dosage will be modified according to the severity of the toxicities. Response to the drug will be followed; progression of disease and/or excessive toxicities will terminate the study for the patient.

#### PROGRESS

No patients entered at MAMC.

STATUS: (O)

TITLE: GOG 26-S: A Phase II Trial of Teniposide in Patients  
with Advanced Pelvic Malignancies

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANTS: COL William Benson, MC

WORK UNIT NO: 84/64

TECHNICAL OBJECTIVE

To determine the efficacy of Teniposide in patients whose advanced malignancies have been resistant to high priority methods of treatment.

METHOD

Teniposide will be administered at a dosage of 100 mg/M<sup>2</sup> every week. The patients will be followed for toxicities to the drug and the drug dosages will be modified according to the severity of the toxicities. Response to the drug will be followed. Progression of disease and/or excessive toxicities will terminate the study for the patient.

PROGRESS

No patients entered at MAMC.

STATUS: (O)

TITLE: GOG #26R: A Phase II Trial of Progesterone in the  
Treatment of Advanced or Recurrent Epithelial Ovarian  
Cancers that Have Failed Combination Chemotherapy

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 84/25

#### TECHNICAL OBJECTIVE

To determine the efficacy of progesterone in patients whose advanced malignancies have been resistant to higher priority methods of treatment.

#### METHOD

All patients with measurable gynecological cancer, who have failed higher priority therapies, will be offered C.T. Provera as a Phase II drug to determine its efficacy. The drug is given at 50 mg (1 tablet) t.i.d until progression of disease.

#### PROGRESS

No patients entered at MAMC.

STATUS: (0)

TITLE: GOG #26Q: A Phase II Trial of Aminothiadiazole in  
Patients with Advanced Pelvic Malignancies

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 83/26

#### TECHNICAL OBJECTIVE

To determine the efficacy of aminothiadiazole in patients whose advanced malignancies have been resistant to high priority methods of treatment.

#### METHOD

All patients with measurable gynecological cancer who have failed higher prior therapies will be offered aminothiadiazole as a Phase II drug to determine its efficacy. The drug will be given as 125 mg/M<sup>2</sup> I.V. once a week. Patients will continue to receive the agent until progression or adverse effects prohibit further therapy.

#### PROGRESS

No patients entered at MAMC.

STATUS: (O)

TITLE: GOG #26P: A Phase II Trial of AT-125 in Patients with  
Advanced Pelvic Malignancies

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 83/25

#### TECHNICAL OBJECTIVE

To determine the efficacy of AT-125 in patients whose advanced malignancies have been resistant to high priority methods of treatment.

#### METHOD

All patients with measurable gynecological cancer who have failed higher prior therapies will be offered AT-125 as a Phase II drug to determine its efficacy. The drug will be given as 12-15 mg/M<sup>2</sup> I.V. daily for five days every three weeks. Patients will continue to receive the agent until progression or adverse effects prohibit further therapy.

#### PROGRESS

No patients entered at MAMC.

STATUS: (0)



TITLE: GOG #49: A Surgical-Pathologic Study of Women with Invasive Carcinoma of the Cervix Stage I<sub>B</sub> and Randomly Assigned Radiation Therapy Versus No Further Therapy in Selected Patients, Phase III

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 81/70

#### TECHNICAL OBJECTIVES

To determine by observations of the 5-year survival and disease-free interval, the validity of current FIGO staging of the histopathologic prognostic factors of size of lesion, location of lesion, depth of invasion of tumor in millimeters, histology and grade, growth pattern, and site and number of positive lymph nodes in Stage I<sub>B</sub> carcinoma of the cervix; to rapidly accumulate prospectively significant surgical pathologic data which would expedite development of further protocols; to determine morbidity of primary radical surgical therapy; to determine if radiation therapy will improve survival in selected patients with positive nodes.

#### METHOD

Patients with primary, previously untreated histologically confirmed invasive Stage I<sub>B</sub> (invasion of 3 mm or greater of lymphatic invasion) carcinoma of the cervix (squamous cell, adenocarcinoma, or adenosquamous) will be eligible. Patients must have undergone exploratory laparotomy, peritoneal fluid sampling, bilateral pelvic and paraaortic lymphadenectomy and radical hysterectomy to be eligible for the randomized portion of the study. Those with negative pelvic nodes will receive no further therapy and be followed for 5 years. Those with positive pelvic nodes, unilateral metastasis, 3 or fewer positive pelvic nodes, no parametrial involvement, and clear vaginal margins will be randomized to receive no further therapy (follow-up for 5 years) or whole pelvic radiation with follow-up of 5 years. Those with positive para-aortic nodes on paraffin section will be entered on other GOG protocols as appropriate.

#### PROGRESS

(3/81 - 9/84) Eight patients were entered on this protocol at MAMC. Three patients died from the cancer, four are alive without evidence of disease, and one was lost to follow-up.

A paper is being prepared for publication by the national group.

STATUS: (C)

TITLE: GOG #50: A Study of Adriamycin as Postoperative Therapy  
for Ovarian Sarcoma, Primary or Recurrent, With no Prior  
Chemotherapy

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 81/71

#### TECHNICAL OBJECTIVES

To evaluate the efficacy of adriamycin in the treatment of primary ovarian sarcomas, primary or recurrent, through historic controls; and to accumulate additional surgical-pathological data relative to ovarian sarcomas.

#### METHOD

Patients must have histologically confirmed primary Stage I-IV or recurrent ovarian sarcoma. Cases without histologic confirmation of recurrence must be documented by submission of original slides. Optimal reductive surgery is required for cases with advanced disease, whether primary or recurrent. Patients may have measurable disease, nonmeasurable disease, or no residual disease postoperatively. The endometrium must be examined to exclude an endometrial origin of the tumor. Patients with prior chemotherapy are ineligible. All patients will receive chemotherapy as soon as the acute effects of surgery have resolved. After completion of a total cumulative dose of 550 mg/M<sup>2</sup>, patients with clinically complete responses or detectable disease which is thought to be resectable will undergo second look surgery. Those patients with progression will be entered on Protocol #26. At second look those with NED will have no further therapy and follow-up for five years; those with stable disease or progression will be entered on Protocol #26.

#### PROGRESS

No entries at MAMC.

STATUS: (0)

TITLE: GOG #52: A Phase III Randomized Study of Cyclophosphamide Plus Adriamycin Plus Platinol Versus Cyclophosphamide Plus Platinol in Patients with Optimal Stage III Ovarian Adenocarcinoma

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 81/105

#### TECHNICAL OBJECTIVES

To determine, in "optimal" Stage III ovarian adenocarcinoma, if the addition of adriamycin to cyclophosphamide plus cis-platinum (Platinol) improves progression-free interval, frequency of negative second-look laparotomy and survival. This protocol replaces GOG #25.

#### METHOD

Eligible patients are those more than six weeks post-operative with proven primary Stage III ovarian adenocarcinoma confined to the abdominal cavity and its peritoneal surfaces with residual tumor masses after surgery no larger than 1 cm in diameter. Patients with prior chemo- or radiotherapy are ineligible. Patients will be randomized to cyclophosphamide plus Plantinol every three weeks for eight courses or to cyclophosphamide and Plantinol plus adriamycin every three weeks for eight courses. After eight courses those with less than clinically complete response will go off study and be followed for survival; those with clinically complete response will have second-look surgery to validate the complete response or to remove residual tumor masses. Patients will then be followed for approximately five years for survival rates.

#### PROGRESS

Three patients were entered in FY 84 for a total of seven entries. One patient died of disease and six are alive without disease.

STATUS: (O)

TITLE: GOG #54: The Treatment of Women with Malignant Tumors of the Ovarian Stroma with Combination Vincristine, Dactinomycin, and Cyclophosphamide--Phase III; and a Phase II Evaluation of Adriamycin in Malignant Tumors of the Ovarian Stroma Refractory to Primary Chemotherapy

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 81/116

#### TECHNICAL OBJECTIVES

To evaluate the effectiveness of combined vincristine, dactinomycin, and cyclophosphamide (VAC) in treatment of malignant tumors of the ovarian stroma in patients with residual, recurrent or advanced disease; to confirm completeness of response to VAC treatment with restaging laparotomy; to evaluate response to adriamycin in patients who fail primary treatment with VAC; to evaluate the endometrium histologically to learn more about the relationship between stromal tumors and endometrial cancer.

#### METHOD

Eligible patients must have histologically confirmed malignant tumors of the ovarian stroma (granulosa cell tumor, granulosa-theca cell tumor, Sertoli-Leydig cell tumor, androblastoma, gynandroblastoma, unclassified sex cord-stromal tumor, sex cord tumor with annular tubules) not amenable to cure by further surgery or radiation therapy. Patients who have received chemotherapy at any time or those who have received radiotherapy less than four weeks prior to entry are ineligible for study. Patients admitted to this study will have undergone an exploratory laparotomy with removal of as much tumor as is prudent. Chemotherapy will be followed within four weeks and not later than six weeks following surgery. Patients must have recovered from surgery. All patients will receive VAC for a minimum of three cycles or a maximum of ten cycles. Patients who exhibit a complete response or a partial response after ten cycles which makes remaining disease resectable will undergo a restaging laparotomy. If all residual disease is resected at restaging laparotomy, patients will receive adriamycin. If there is no evidence of disease at restaging laparotomy, patients will receive intermittent cyclophosphamide. If progression is observed during cyclophosphamide therapy, patient will be removed from study. Patients who exhibit progression of disease after three cycles of VAC will receive adriamycin. If further progression is observed on adriamycin therapy, the patient will be removed from the study. All patients will be followed for five years or until death.

#### PROGRESS

One patient entered during FY 84; alive without evidence of disease.

STATUS: (0)

TITLE: GOG #55: Hormonal Contraception and Trophoblastic Sequelae  
After Hydatidiform Mole, Phase III

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 81/44

#### TECHNICAL OBJECTIVES

To determine whether the administration of estrogen progesterone oral contraceptives following the evacuation of a hydatidiform mole and prior to the HCG titer reaching undetectable levels affects the incidence of trophoblastic sequelae requiring chemotherapy.

#### METHOD

Patients with a histologically verified diagnosis of hydatidiform mole evacuated by suction evacuation of the uterus with uterine conservation are eligible. All patients must have a pelvic ultrasound and arterial blood gases performed within 2 weeks of evacuation. Patients will be randomly assigned to Regimen 1: hormonal contraception - oral contraception to be commenced as soon as the patient has been randomized and will continue for at least 12 weeks; or Regimen 2: mechanical contraception - a. sheath and foam preparation; b. IUD inserted once the uterus has become involuted, again used with foam; c. diaphragm used with contraceptive cream or foam. The principal investigator will choose the method of mechanical contraception and it will be commenced as soon as the patient has been randomized and will continue for at least 12 weeks. At the end of 12 weeks, all patients will be evaluated for development or nondevelopment of trophoblastic sequelae. Further birth control will be at the discretion of the patient and the investigator. All patients will remain on the study for a minimum of six months after primary evacuation of the molar pregnancy.

#### PROGRESS

Two entries in FY 84 at MAMC for a total of four subjects. All are alive with no evidence of disease.

STATUS: (0)

TITLE: GOG #56: A Randomized Comparison of Hydroxyurea Versus Misonidazole as an Adjunct to Radiation Therapy in Patients with Stage II<sub>B</sub>, III, and IV<sub>A</sub> Carcinoma of the Cervix and Negative Para-Aortic Nodes (Phase III)

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANTS: COL William L. Benson, MC  
COL Donald Kull, MC

WORK UNIT NO: 82/08

#### TECHNICAL OBJECTIVE

To determine whether hydroxyurea or misonidazole is superior as a potentiation of radiation therapy in advanced cervical cancer; and to compare the toxicity of hydroxyurea versus misonidazole when given concurrently with radiotherapy.

#### METHOD

All patients with invasive squamous cell carcinoma of the cervix, Stages II<sub>B</sub> through IV<sub>A</sub> will undergo preoperative clinical staging. This will include traditional staging as permitted by FIGO rules. Extended clinical staging utilizing lymphangiography, computerized transaxial tomography, and/or sonography is required. Subsequently, patients will undergo a para-aortic lymphadenectomy and peritoneal exploration. Selected patients may be excluded from this procedure if percutaneous needle biopsy provides histologic proof of metastasis to the aortic nodes. All patients with cancer confined to the pelvis are eligible for treatment. They will receive pelvic irradiation and will be randomly assigned to receive concomitant hydroxyurea or misonidazole. Patients with metastasis outside the pelvis are not eligible for treatment.

#### PROGRESS

Three entries at MAMC during FY 84. One patient died from cancer and two are alive with no evidence of disease.

STATUS: (O)

TITLE: GOG #57: A Randomized Comparison of Multiple Agent Chemotherapy with Methotrexate, Dactinomycin, and Chlorambucil versus the Modified Bagshawe Protocol in the Treatment of "Poor Prognosis" Metastatic Gestational Trophoblastic Disease (Phase II)

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANTS: COL William L. Benson, MC

WORK UNIT NO: 82/31

#### TECHNICAL OBJECTIVE

To evaluate the effectiveness and toxicity of the Modified Bagshawe Protocol (MBP) in patients with "poor prognosis" metastatic gestational trophoblastic disease (MGTD); and to compare the effectiveness and toxicity of the MBP with standard triple agent chemotherapy with methotrexate, dactinomycin, and chlorambucil (MAC).

#### METHOD

Patients who have a histologic diagnosis of gestational trophoblastic disease and an elevated HCT titer, who are considered "poor prognosis" on the basis of the criteria set forth in the protocol, will be randomized to either a drug combination of MAC or to a modified Bagshawe Protocol.

#### PROGRESS

No entries at MAMC during FY 84. One patient entered (FY 83) with a complete response to the Bagshawe regimen.

STATUS: (O)

TITLE: GOG #59: A Randomized Comparison of Extended Field Radiation Therapy and Hydroxyurea Followed by Cisplatin or no Further Therapy in Patients with Cervical Squamous Cell Carcinoma Metastatic to High Common Iliac and/or Para-aortic Lymph Nodes--III

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC  
COL Donald Kull, MC

WORK UNIT NO: 81/117

#### TECHNICAL OBJECTIVES

To determine if cis-diamminedichloroplatinum, cisplatin, given in an adjuvant setting will decrease the risk of geographic failure or improve the survival rate or progression-free interval in patients who have squamous carcinoma of the cervix with metastases to high common iliac and/or para-aortic lymph nodes, proven by either histologic or cytologic means; to evaluate the role of scalene fat pad biopsy in this group of patients before initiation of extended field irradiation therapy; to accumulate clinical/surgical pathologic data on this highrisk group of patients to expedite development of further protocols.

#### METHOD

Eligibility: All patients with primary, previously untreated, histologically confirmed, invasive squamous cell carcinoma of the uterine cervix, all clinical stages, with metastasis to high common iliac or para-aortic lymph nodes proven by cytologic or histologic means. Patients will undergo preoperative clinical staging (stages defined in protocol) utilizing lymphangiography, computerized axial tomography, and/or sonography as well as traditional methods. Subsequently, the patients will undergo a para-aortic lymphadenectomy and peritoneal exploration. Selected patients may be excluded from this procedure if percutaneous needle biopsy provides cytologic proof of metastasis to extra-pelvic nodes. All patients with para-aortic metastasis and negative scalene node biopsies are eligible for treatment. They will receive pelvic and para-aortic irradiation and hydroxyurea and will be randomly assigned to receive cisplatin or no further therapy. An adequate trial will be defined as completion of the prescribed radiation therapy, completion of one course of cisplatin and survival of four weeks, or survival of eight weeks after radiation therapy for the no-further-treatment regimen. Patients will be followed quarterly for two years and every six months for three additional years.

#### PROGRESS

One entry at MAMC on the cis-platin arm with no evidence of disease.

STATUS: (O)



TITLE: GOG #60: A Phase III Randomized Study of Doxorubicin Plus Cyclophosphamide Plus Cisplatin versus Doxorubicin Plus Cyclophosphamide Plus Cisplatin Plus BCG in Patients with Advanced Suboptimal Ovarian Adenocarcinoma, Stage III and IV.

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 81/118

#### TECHNICAL OBJECTIVES

To determine if the addition of BCG to doxorubicin plus cyclophosphamide plus cisplatin improves remission rate, remission duration, or survival in suboptimal Stage III and Stage IV ovarian adenocarcinoma; to determine the frequency and duration of true complete remission using these regimens as judged at second-look laparotomy.

#### METHOD

Eligibility: Patients with established suboptimal Stage III or Stage IV ovarian epithelial cancer. Patients must have optimal surgery for ovarian cancer, with at least an exploratory laparotomy and appropriate tissue for histologic evaluation. Patients with measurable or nonmeasurable disease will be evaluated. Patients with histologically confirmed serous adenocarcinoma, mucinous adenocarcinoma, clear-cell adenocarcinoma, endometrioid adenocarcinoma, undifferentiated carcinoma, or mixed epithelial carcinoma will be eligible. Patients who have received previous chemotherapy or radiotherapy will be ineligible. Patients will be randomized to receive either doxorubicin, cyclophosphamide, and cisplatin every 3 weeks for 8 courses; or the above regimen plus BCG (days 8 & 15 for 8 courses). Patients with complete response will have a second look laparotomy and will be taken off therapy if complete response is confirmed. Patients who have partial response of stable disease will be considered for a second look if, in the opinion of the investigator, significant tumor reduction may have been achieved. If residual tumor is detected, patients will be taken off study and placed on GOG #61. Patients with progressive disease at any time will be removed from the chemotherapy on this study, but will be followed.

#### PROGRESS

(82 09 - 83 09) Two patients were entered in FY 84 for a total of six entries. One patient expired from a pulmonary embolus, one refused BCG after scarifications after two separate times, had recurrent carcinoma, and expired, and the other four patients are alive without disease.

STATUS: (O)

TITLE: GOG #61: Phase III Randomized Study of Cis-Platinum Plus Cyclophosphamide versus Hexamethylmelamine After SecondLook Surgery in Nonmeasurable Stage III Ovarian Adenocarcinoma Partially Responsive to Previous Regimens Containing Cis-Platinum and Cyclophosphamide.

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 82/09

#### TECHNICAL OBJECTIVE

To determine in nonmeasurable but residual Stage III ovarian adenocarcinoma, partially responsive after treatment with regimens containing cis-platinum and cyclophosphamide, if the progression-free interval and survival are improved by continuing cyclophosphamide plus cis-platinum or by changing treatment to hexamethylmelamine.

#### METHOD

With the increasing use of second-look laparotomy after combination chemotherapy for ovarian cancer, more Stage III patients are being identified who show a partial response or stable disease when compared with the original findings. The GOG has two studies involving cyclophosphamide and cis-platinum, but not hexamethylmelamine (Protocols #47 and #52), in which partial responders (as judged at second look) currently go off study. We propose to randomize such patients to more cyclophosphamide plus cis-platinum or to hexamethylmelamine. This additional treatment will be given for a finite period of 12 months since we do not propose a third look that might provide an endpoint for treatment but probably would not benefit most patients as there is no promising third line treatment if residual disease were found and it is unlikely that debulking surgery would be of consistent benefit at this point and it may be difficult to do adequate biopsies after two prior laparotomies. Also, some of these patients may progress slowly even though they do not respond to the additional treatments.

#### PROGRESS

(82 10 - 83 09) Two patients entered at MAMC during FY 84 for a total of four entries. Two patients have died from cancer, one patient is alive with cancer, and one patient is alive without disease.

STATUS: (0)

TITLE: GOG #63: A Clinical-Pathologic Study of Stages II<sub>B</sub>, III,  
and IV<sub>A</sub> Carcinoma of the Cervix

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 82/36

#### TECHNICAL OBJECTIVES

To evaluate the sensitivity and specificity of non-invasive procedures such as sonography, computerized transaxial tomography and lymphangiography in detection of metastases; to better understand the significance of various surgical and pathologic factors involved in staging and therapy for "advanced" cervical cancer. The accumulated clinical/surgical/pathological data may then play a role in modification or design of future protocols; to determine by observations of five-year survival and disease-free interval, the validity of current FIGO staging in comparison to histopathologic prognostic factors such as size of lesion, location of lesion, histology, grade, pelvic lymph node metastases, and aortic lymph node metastases, in patients with Stages II<sub>B</sub>, III, and IV<sub>A</sub> carcinoma of the cervix.

#### METHOD

All eligible patients with invasive carcinoma of the cervix, Stages II<sub>B</sub> through IV<sub>A</sub>, will undergo preoperative clinical staging, including traditional staging as permitted by FIGO rules. Extended clinical staging utilizing sonography, lymphangiography, and computerized transaxial tomography are mandatory. When these tests reveal an aortic nodal metastasis, the patient will have a fine needle biopsy; however, if the tests are negative, the patient will have an aortic lymphadenectomy. Patients who have a positive fine needle biopsy or positive aortic lymphadenectomy will undergo scalene node biopsy before consideration for a GOG treatment protocol. It is anticipated that all patients will be considered for entry into a GOG protocol for which they are suitable when such protocols are available.

#### PROGRESS

Two entries at MAMC during FY 84. Both patients are alive without evidence of disease.

STATUS: (0)

TITLE: GOG #64: A Randomized Comparison of Rapid vs Prolonged  
(24-Hour) Infusion of Cisplatin in Therapy of Squamous  
Cell Carcinoma of the Cervix.

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 82/37

#### TECHNICAL OBJECTIVES

(1) To determine whether the frequency and duration of objective response of squamous cell carcinoma of the cervix is altered significantly by prolonging to 24 hours the duration of the infusion of a dose of cisplatin as compared to administration at a rate of 1 mg/minute; and (2) to determine whether the administration of a dose of cisplatin as a continuous 24-hour infusion alters the frequency and/or severity of drug-related nausea and vomiting as compared to the administration of the same dose at a rate of 1 mg/minute.

#### METHOD

Eligible patients are those with histologically confirmed, locally advanced, recurrent, persistent, or metastatic squamous cell carcinoma of the cervix which is resistant to curative treatment with surgery or radiotherapy. Cis-platinum (50 mg/M<sup>2</sup>) will be given as a 24-hour infusion or at a rate of 1 mg/minute IV once every three weeks. Treatment will be repeated every three weeks for eight courses unless disease progression or adverse effects dictate cessation.

#### PROGRESS

No patients entered during FY 84. One patient was entered in FY 83. There was no response to cis-platinum and the patient died from the cancer.

STATUS: (0)

TITLE: GOG #66: Ultrastructural, Staging, and Therapeutic  
Considerations in Small Cell Carcinoma of the Cervix,  
Phase II

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANTS: COL William Benson, MC

WORK UNIT NO: 83/40

#### TECHNICAL OBJECTIVE

To determine the incidence of neuroendocrine carcinoma of the cervix in cases which are histologically classified as small cell carcinomas, and to determine the response rate to combination chemotherapy in patients with Stage IVB small cell carcinoma of the cervix or progressive local disease after radiation therapy.

#### METHOD

Eligible patients: Those with histologic diagnosis of small cell carcinoma of the cervix. Patients who have small cell carcinoma mixed with large cell keratinizing carcinoma or large cell non-keratinizing carcinoma or adenocarcinoma are eligible, providing that the small cell elements comprise 50% of the tumor. Only patients with primary Stage IVB disease or recurrent disease after local therapy are eligible for chemotherapy. Chemotherapy patients must have measurable disease by palpation or by an appropriate x-ray or ultrasound procedure.

Patients with disease localized to the pelvis and regional lymph nodes will receive standard therapy according to the discretion of the investigator. Patients with disease beyond the pelvis or abdominal nodes with no previous irradiation will receive vincristine, 2 mg, doxorubicin, 50 mg/M<sup>2</sup>, and cyclophosphamide, 750 mg/M<sup>2</sup>, intravenously every 21 days. Patients with previous irradiation will receive vincristine, 2 mg, doxorubicin, 40 mg/M<sup>2</sup>, and cyclophosphamide, 600 mg/M<sup>2</sup>, intravenously every 21 days. These regimens will be repeated every three weeks if toxicity permits. Doxorubicin will be discontinued at a cumulative dose of 400 mg/M<sup>2</sup>. Patients in whom tumor progression occurs on this regimen will be treated with VP-16, 100 mg/M<sup>2</sup> (no previous irradiation) or 80 mg/M<sup>2</sup> (previous irradiation) intravenously on days 1, 3, and 5, every four weeks to time of progression. Patients will be followed until expiration or for five years. In the unusual instance of Stage IVB on the basis of brain metastasis alone, patients will be given whole brain irradiation to a dose of 3000 rads in 10 fractions.

#### PROGRESS

No entries at MAMC.

STATUS: (0)

TITLE: GOG #70: A Randomized Comparison of Single Agent Chemotherapy (Methotrexate and Methotrexate with Folinic Acid Rescue) in "Good Prognosis" Metastatic Gestational Trophoblastic Disease

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANTS: COL William Benson, MC

WORK UNIT NO: 83/63

#### TECHNICAL OBJECTIVES

To judge the relative efficacy of scheduling variation in the chemotherapeutic management of "good prognosis" metastatic gestational trophoblastic disease and to ascertain the relative toxicities of the two regimens.

#### METHOD

Eligible patients: those with metastatic gestational trophoblastic disease who are "good prognosis" with duration of disease <4 months from antecedent pregnancy, serum  $\beta$ -hcg titer <42,000 mIU/ml, no liver or brain metastasis, no prior chemotherapy, and antecedent molar pregnancy, ectopic pregnancy, or abortion.

Regimen I: methotrexate 0.4 mg/kg IM, up to 25 mg daily x 5; repeat every 12 days (7 day window).

Regimen II: methotrexate, 1 mg/kg IM, days 1, 3, 5, and 7. Folinic acid, 0.1 mg/kg, IM, days 2, 4, 6, and 8. Repeat every 14 days (6 day window).

An adequate trial is defined as receiving one course. After the first normal titer (three consecutive weekly normals), each patient will receive one more full course. If she attains remission, therapy will be discontinued. If the titer should re-elevate prior to three consecutive weekly normals, then chemotherapy will continue until the above criteria are fulfilled. All patients will receive chemotherapy as outlined until there is documented remission, severity of toxicity requires a change, or non-response.

#### PROGRESS

No patients entered at MAMC during FY 84. One patient was entered during FY 83 and is currently free of disease.

STATUS: (0)

TITLE: NCI #7602: All Stage I<sub>C</sub> and II (A, B, C) and Selected Stage I<sub>Aii</sub> and I<sub>Bii</sub> Ovarian Cancer

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANTS: COL William L. Benson, MC

WORK UNIT: 81/33

#### TECHNICAL OBJECTIVE

To define the natural history of patients treated by surgery plus either chemotherapy or radioisotope; to study the effect of various potential prognostic factors on the natural history of patients treated by each form of therapy; to determine the patterns of relapse for each form of therapy; to establish the value of various staging parameters on the stage of disease and its natural history.

#### METHOD

All patients with common epithelial ovarian cancer are eligible, if after definitive staging procedures the patient is zoned to be in Stages 2<sub>A</sub>, 2<sub>B</sub>, 2<sub>C</sub>, 1<sub>Aii</sub>, 1<sub>Bii</sub>, or 1<sub>Ai</sub> or 1<sub>Bi</sub> with poorly differentiated tumors. Patients with prior therapy are ineligible. Patients will be stratified by histology, histological grade, and stage group for Regimen I. Regimen I will have staging laparotomy, total abdominal hysterectomy and bilateral salpingo-oophorectomy with no macroscopic residual disease found. Patients will then be randomized to receive melphalan or radioisotopes. Regimen II will be stratified by histology, histological grade, and extent of disease after surgery. Patients will have staging laparotomy, total abdominal hysterectomy, and bilateral salpingo-oophorectomy. If II<sub>B</sub>, II<sub>C</sub>, residual disease is found, patient will be randomized to pelvic radiotherapy plus melphalan alone. If after 18 months of therapy, the patient remains free of disease, chemotherapy will be discontinued. Second look will be done if the patient is free of disease after 18 months of chemotherapy.

#### PROGRESS

No patients entered during FY 84. One patient was entered in FY 81.

STATUS: (0)

LE: NCI #7601 - Selected Stage I<sub>A1</sub> - I<sub>B1</sub> Ovarian Cancer  
(Well and Moderately Differentiated)

NCIPAL INVESTIGATOR: COL Roger B. Lee, MC

FESSIONAL ASSISTANTS: COL William L. Benson, MC

K UNIT: 81/45

#### TECHNICAL OBJECTIVE

define the natural history of patients treated by surgery; determine whether prophylactic, adjuvant chemotherapy with phalan alters the natural history; to study the effect of ious potential prognostic factors on the natural history of ients treated by each form of therapy; to establish the ue of various staging parameters on the stage of disease its natural history.

#### METHOD

be eligible, patients must have a histopathologic diagnosis common epithelial ovarian cancer, either serous, mucinous, other (endometrioid, transitional, mesonephroid, adenocanthoma, tures and intermediate types, and unclassifiable). Patients l be stratified by histology, histologic grade, and stage. er staging laparotomy and total abdominal hysterectomy or ateral salpingo-oophorectomy, patients will be randomized observation with no chemotherapy or to a chemotherapy regimen nelphalen (0.2 mg/kg/day PO for 5 days). The chemotherapy l be repeated every four weeks for 18 months or after 12 les of therapy, whichever comes first. Chemotherapy will discontinued for unacceptable toxicity or at 18 months if patient is free of disease at that time. If patient apses, she will be taken off study at that time. Second-look l occur at 18 months after randomization using peritoneoscopy laparotomy.

#### PROGRESS

entries at MAMC.

FUS: (O)



TITLE: NCI #180-12: Group C Guidelines for the Use of Delta-9-Tetrahydrocannabinol

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC Irwin B. Dabe, MC  
LTC Alan D. Mease, MC  
MAJ Lauren K. Colman, MC

WORK UNIT: 81/102

#### TECHNICAL OBJECTIVE

To determine untoward side effects not previously described with THC and to make available this antinausea drug to patients on chemotherapy.

#### METHOD

Delta-9-THC will be used as an antiemetic therapy in cancer chemotherapy patients refractory to standard antiemetic agents. It will be administered at a starting dose of 5 mg/m<sup>2</sup> p.o., 6-8 hours prior to the administration of chemotherapy and for 12 hours thereafter. Should the 5 mg/m<sup>2</sup> dose prove to be ineffective, and in the absence of significant side effects, the dose may be escalated to 7.5 mg/m<sup>2</sup>. Any untoward side effects will be reported to the NCI.

#### PROGRESS

No new entries at MAMC in FY 84. Of 11 entries in previous years, drowsiness was the only reported side effect.

STATUS: (O)

TITLE: NCI #180-11: VP-16-312 For Small Cell Carcinoma of the Lung (Group C Guidelines)

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC Irwin B. Dabe, MC  
LTC Archie W. Brown, MC

WORK UNIT: 81/20

#### TECHNICAL OBJECTIVE

To provide an investigational drug of proven efficacy, not previously released for general use, to MAMC patients under Group C NCI Guidelines. To determine extent and variety of side effects with VP-16-312 that have not been previously described.

#### METHOD

VP 16-312 will be used in refractory or recurrent small cell cancer of the lung, usually in combination with other effective chemotherapeutic drugs. It will be administered IV over a 30-minute period either daily for 5 days every 2-3 weeks or on days 1, 3, and 5 every 4-5 weeks. The exact interval between subsequent courses will be modified, depending on the time required for recovery from toxic manifestations. Careful pre-treatment evaluation and follow-up will be done. Any untoward or unexpected side effects will be reported to the NCI. The treatment will be continued for as long as the patient's tumor responds or remains stable.

#### PROGRESS

(12/80 - 12/83) Five patients were entered on this protocol in FY 84 for a total of 19 entries at MAMC. Neutropenia, thrombocytopenia, hair loss, anemia, and fatigue (expected side effects of the small cell carcinoma of the lung and the chemotherapy) were reported. The drug has now been released by the FDA.

STATUS: (C)

TITLE: NCI #I78-10: Guidelines for the Clinical Use of  
Hexamethylmelamine (Group C Guidelines)

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: COL Roger B. Lee, MC  
LTC Archie W. Brown, MC  
LTC Irwin B. Dabe, MC

WORK UNIT: 81/19

#### TECHNICAL OBJECTIVE

To provide an investigational drug of proven efficacy, not previously released for general use, to MAMC patients under Group C NCI Guidelines. Also to determine the extent and variety of side effects with hexamethylmelamine that have not been previously described.

#### METHOD

Hexamethylmelamine will be used in patients whose cancer of the ovary has become refractory to therapy with alkylating agents or in patients where therapy with alkylating agents is contra-indicated. Hexamethylmelamine will be given daily by mouth, either continuously or intermittently depending on response, toxicity, and other drugs which the patient may be taking concomitantly. The treatment will continue for as long as the disease is stable or the tumor shrinks.

#### PROGRESS

No new patients were entered on this protocol in FY 84. Eight entries in previous years. Nausea and neutropenia were reported as adverse reactions.

STATUS: (O)

TITLE: NCI #I78-4: Guidelines for the Clinical Use of  
Streptozotocin (Group C Guidelines)

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC Irwin B. Dabe, MC  
LTC Archie W. Brown, MC

WORK UNIT: 81/18

#### TECHNICAL OBJECTIVE

To provide an investigational drug of proven efficacy, not previously released for general use, to MAMC patients under Group C NCI Guidelines. Also, to determine extent and variety of side effects with streptozotocin that have not been previously described.

#### METHOD

Streptozotocin will be used for patients with malignant islet cell tumor (response rate 70%) and in metastatic carcinoid. Streptozotocin will be given IV either daily for 5 days every 4-6 weeks or weekly for approximately 4 weeks. Careful pre-treatment evaluation will be accomplished and any untoward or unexpected side effects will be reported to the National Cancer Institute.

#### PROGRESS

(80-12 - 83 09) No entries at MAMC.

STATUS: (0)

D E T A I L   S H E E T S  
F O R  
P R O T O C O L S

NATIONAL CANCER INSTITUTE PROTOCOLS

TITLE: GOG 78: Evaluation of Adjuvant Vinblastine, Bleomycin, and Cisplatin Therapy in Totally Resected Choriocarcinoma, Endodermal Sinus Tumor, or Embryonal Carcinoma of the Ovary, Pure and Mixed with Other Elements

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANTS: COL William L. Benson, MC

WORK UNIT NO: 84/74

#### TECHNICAL OBJECTIVES

To evaluate the effect of adjuvant vinblastine, bleomycin, and cisplatin (VBP) chemotherapy in patients with endodermal sinus tumor and choriocarcinoma of the ovary (pure and mixed) after removal of all gross tumor; to evaluate the role of serum markers, especially alphafetoprotein and human chorionic gonadotropin, in predicting recurrence; to evaluate the role of reassessment laparotomy in determining response, detecting early relapse, and planning further therapy; and to compare the biologic behavior of pure endodermal sinus tumors with mixed germ cell tumors containing endodermal sinus elements.

#### METHOD

Patients with totally resected Stage I choriocarcinoma, endodermal sinus tumor, or embryonal carcinoma of the ovary with negative peritoneal washings, normal (or falling at a rate that does not suggest residual disease) serum AFP and beta-HCG levels, and adequate bone marrow, renal, and hepatic function will be studied. Stages II and III will also be eligible if all gross tumor is resected. After recovery from surgery, patients will receive 3 cycles of VBP therapy. Patients who show evidence of progression while on VBP therapy will be candidates for GOG Protocol 26. Patients completing three cycles of treatment clinically free of disease will undergo reassessment laparotomy. Patients with recurrent disease at reassessment laparotomy will be candidates for GOG Protocol 26. To be evaluable a patient will receive at least one week of chemotherapy and live another two weeks. Each patient will remain on study until adverse effects prohibit further therapy or until evidence of progression is noted.

#### PROGRESS

No entries at MAMC.

STATUS: (O)

TITLE: GOG #77: A Randomized Study of Carboplatin (CBDCA-NSC #241240) Versus CHIP (NSC #256927) In Advanced Carcinoma of the Cervix

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 84/29

#### TECHNICAL OBJECTIVE

To determine the objective response rate of squamous cell carcinoma of the cervix to Carboplatin and to CHIP; to determine in a randomized study whether Carboplatin or CHIP has a superior (statistically significant) objective response rate in cervical carcinoma; and to assess and compare toxicity (gastrointestinal and renal) of Carboplatin and CHIP.

#### METHOD

Eligible: patients who have histologically confirmed, locally advanced, recurrent, persistent, or metastatic squamous cell carcinoma of the cervix resistant to curative treatment with surgery or radiotherapy.

Regimen I: Carboplatin will be given 400 mg/M<sup>2</sup> as a 15 min IV infusion once every four weeks.

Regimen II: CHIP will be given 300 mg/M<sup>2</sup> as a 2 hr infusion once every four weeks.

Both treatments will continue until disease progresses or until toxicity prohibits further therapy. Survival status will continue to death.

#### PROGRESS

(1/84 - 9/84) Three patients were entered at MAMC. Two died of their disease and one is alive and free of disease.

A paper is being prepared by the national group.

STATUS: (C)

TITLE: GOG #75: Postoperative Pelvic Radiation in Stages I  
and II Mixed Mesodermal Sarcomas of the Uterus

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANTS: COL Willlliam L. Benson, MC

WORK UNIT NO: 84/28

#### TECHNICAL OBJECTIVE

To determine if pelvic postoperative radiation therapy will decrease local and regional recurrence rates and improve median progression free interval in patients with Stages I and II mixed mesodermal sarcomas of the uterus.

#### METHOD

Patients with clinical Stage I or II mixed mesodermal sarcomas of the uterus undergoing a simple extrafascial abdominal hysterectomy, bilateral salpingo-oophorectomy, or selective pelvic or para-aortic lymphadenectomy will be randomized to receive postoperative radiation therapy or no further treatment. The principal parameters employed to examine the therapeutic effect of postoperative pelvic radiation are local and regional recurrence rates, the duration of progression-free interval, observed survival time and the incidence and severity of observed adverse effects. The patients will be followed until death or for at least ten years.

#### PROGRESS

No entries at MAMC.

STATUS: (0)



TITLE: GOG #74: Early Stage I Vulvar Carcinoma Treated With  
Ipsilateral Superficial Inguinal Lymphadenectomy and  
Modified Radical Hemivulvectomy

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 84/27

#### TECHNICAL OBJECTIVES

To document the rates and patterns of recurrence of patients with early Stage I vulvar carcinoma treated with ipsilateral superficial inguinal lymphadenectomy and modified radical hemivulvectomy and to document the survival and recurrence-free interval in the same group of patients.

#### METHOD

Patients who present with primary, untreated, squamous cell carcinoma of the vulva, with no capillary space involvement, and with a lesion measured *in vivo* < 2 cm, and with histologic evidence of invasion below the basement membrane <5 mm, will be eligible for further evaluation and entry into this protocol. If the frozen section on the superficial inguinal lymph nodes reveals no evidence of cancer, the patient will go on to have a modified radical hemivulvectomy. If the patient has positive lymph nodes on frozen section, she can be treated with radical vulvectomy and bilateral groin dissection per GOG Protocols 36 and 37 (pages 236 and 237 of this report). If the final pathology section shows metastatic carcinoma to nodes, the patient can be treated with radical vulvectomy and bilateral groin dissection, per protocols 36 and 37, the surgery to be carried out within six weeks of the time of the initial groin dissection. The patient will be followed every three months for the first two years and every six months for three additional years. The principal parameters employed to examine the therapeutic effect of hemivulvectomy will be progression-free interval, survival time, and observed adverse effects.

#### PROGRESS

No entries at MAMC.

STATUS: (O)

TITLE: GOG #73: A Clinicopathologic Study of Primary Malignant Melanoma of the Vulva Treated by Modified Radical Hemivulvectomy

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANT: COL William L. Benson, MC

WORK UNIT NO: 84/26

#### TECHNICAL OBJECTIVES

To determine the relationship of histopathologic parameters (including microstaging of primary malignant melanoma of the vulva) to FIGO staging, nodal status, and ultimate prognosis and to ultimately recommend appropriate therapy for malignant melanomas of the vulva based on histopathologic and microstaging data.

#### METHOD

Patients receiving primary surgical therapy for primary malignant melanoma of the vulva with at least a modified radical hemivulvectomy will be studied. Patients with a history of primary cutaneous melanoma other than of genital tract origin or patients who have received previous chemotherapy or radiotherapy are ineligible. The primary parameters to be studied are maximum diameter of the primary lesion, depth of invasion, initial surgical management (including lymph node dissection), nodal status, FIGO staging, microstaging, progression-free interval, and survival probability. Collected data will be used in an attempt to identify possible prognostic factors. Specific statistical goals will be defined as experience is gained.

#### PROGRESS

No entries at MAMC.

STATUS: (0)

TITLE: GOG #72: Ovarian Tumors of Low Malignant Potential: A Study of the Natural History and A Phase II Trial of Melphalan and Secondary Treatment with Cisplatin in Patients with Progressive Disease

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANTS: COL William L. Benson, MC

WORK UNIT NO: 84/33

#### TECHNICAL OBJECTIVES

To evaluate the biologic behavior of ovarian tumors of low malignant potential; to evaluate the effectiveness of chemotherapy against this disease (initially, a Phase II study of melphalan); and to evaluate the response rate to cisplatin in melphalan failures.

#### METHOD

Patients without prior chemotherapy or radiotherapy who have had adequate surgical staging will be eligible. Patients with no grossly visible residual disease will receive no treatment and be followed for 5 years if there is no subsequent disease. If there is no grossly visible clinically apparent residual for 12 months, the patients will have second look surgery and then proceed to melphalan treatment (5 days every four weeks) or follow-up (complete response). With progression after melphalan, patients will proceed to third look and cis-platin treatment (once every three weeks for eight weeks) or follow-up. If there is no evidence or response after three courses of cis-platin, the treatment will be discontinued. Patients who have progression during the first 12 months will be treated as above except they will proceed directly to melphalan treatment without second look surgery. Follow-up will be for a minimum of five years with clinical examination every three months for the first two years, then every six months thereafter.

#### PROGRESS

One patient entered; free of disease.

STATUS: (0)

TITLE: GOG #71: Treatment of Patients with Suboptimal Stage IB Carcinoma of the Cervix: A Randomized Comparison of Radiation Therapy and Post-Treatment Para-Aortic and Common Iliac Lymphadenectomy, Versus Radiation Therapy, Para-Aortic and Common Iliac Lymphadenectomy and Adjunctive Extrafascial Hysterectomy, Phase III

PRINCIPAL INVESTIGATOR: COL Roger B. Lee, MC

PROFESSIONAL ASSISTANTS: COL William Benson, MC  
COL Donald Kull, MC

WORK UNIT NO: 83/41

#### TECHNICAL OBJECTIVES

To evaluate the role of adjunctive extrafascial hysterectomy in the treatment of suboptimal Stage IB carcinoma of the cervix, the survival and patterns of failure in bulky IB cervix cancer, and the prognostic value of pretreatment endometrial sampling in suboptimal Stage IB carcinoma of the cervix; and to study the toxicity of a combined radiation and surgical therapeutic program.

#### METHOD

Eligible patients: patients with primary, untreated, histologically confirmed invasive carcinoma of the uterine cervix, FIGO Stage IB, as confirmed by cervical biopsy and endometrial sampling.

Regimen I: Following recovery from radiation therapy, patients will undergo para-aortic and common iliac nodal sampling, abdominal washings, and intra-abdominal exploration.

Regimen II: Following recovery from radiation therapy, patients will undergo para-aortic and common iliac nodal sampling, abdominal washings, and intra-abdominal exploration plus total extrafascial hysterectomy.

All patients will be followed for five years. Patients found to have more extensive disease (i.e., positive para-aortic nodes, intra-abdominal metastasis) will be treated at the discretion of the physician and will be followed for five years.

#### PROGRESS

No entries at MAMC.

STATUS: (0)

D E T A I L   S H E E T S

F O R

P R O T O C O L S

SOUTHWEST ONCOLOGY GROUP PROTOCOLS

TITLE: SWOG 7804: Adjuvant Chemotherapy with 5-Fluorouracil, Adriamycin, and Mitomycin-C (FAM) vs Surgery Alone for Patients with Locally Advanced Gastric Adenocarcinoma

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC James E. Congdon, MC  
LTC Irwin B. Dabe, MC

WORK UNIT NO: 78/42

#### TECHNICAL OBJECTIVE

To determine the efficacy of adjuvant chemotherapy with FAM on the disease-free interval and survival of patients with TNM stage-groups I<sub>B</sub>, I<sub>C</sub>, II and III gastric adenocarcinoma compared to potentially curative surgery alone.

#### METHOD

Patient Eligibility: patients must have TNM stage-group I<sub>B</sub>, I<sub>C</sub>, II, or III gastric adenocarcinoma and no microscopic or gross residual postoperatively; no prior chemo- or radiotherapy; no medical contraindications to chemotherapy with FAM; serum bilirubin <2.0 mg/100 ml; SGOT and SGPT less than three times the upper limit of normal values; creatinine clearance >75 cc/min; BUN <25 mg%; serum creatinine <1.5 mg%; WBC >4,000; and platelets >100,000.

Treatment: After surgery, patients will be randomized to either Treatment 1 (no further therapy) or Treatment 2:  
FAM - 5-FU, 600 mg/M<sup>2</sup> IV days 1 & 8, 29 & 36  
adriamycin, 30 mg/M<sup>2</sup> IV days 1 & 29  
mitomycin-C, 10 mg/M<sup>2</sup> IV day 1

A total of 6 courses, one every 8 weeks, will be administered. After 12 months, the active therapy phase is completed. The patient will be followed at six month intervals for five years if remission continues.

#### PROGRESS

One entry in FY 84 at MAMC on the observation arm. No recurrence from August 84 to October 84.

STATUS: (0)

TITLE: SWOG 7808, Combination Modality Treatment for Stages  
III and IV Hodgkin's Disease, MOPP #6

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC James E. Congdon, MC  
LTC Irwin B. Dabe, MC

WORK UNIT NO: 78/47

#### TECHNICAL OBJECTIVE

To attempt to increase the complete remission rate induced with MOP-BAP (nitrogen mustard, vincristine, procarbazine, prednisone, adriamycin, and bleomycin) alone utilizing involved field radiotherapy in patients with Stages III and IV Hodgkin's disease achieving partial remission at the end of 6 cycles; and to determine if immunotherapy maintenance with levamisole or consolidation with low dose involved field radiotherapy will produce significantly longer remission durations over a no further treatment group when complete remission has been induced with 6 cycles of MOP-BAP in Stages III & IV Hodgkin's.

#### METHOD

Patients (>15 yrs) must have histologic diagnosis of Hodgkin's disease; no prior chemotherapy. Patients with a history of congestive heart failure, valvular heart disease, or serious obstructive or restrictive pulmonary disease will be excluded.

Treatment 1: Normal marrow patients will receive 6 cycles of MOP-BAP.  
Treatment 2: Impaired bone marrow patients will receive 6 cycles of MOP-BAP with dose modifications.

Complete remission (CR) patients with prior radiotherapy will be randomized between Treatment 3 (no treatment) and Treatment 4 (levamisole). CR patients without prior radiotherapy will receive Treatment 5 (radiotherapy). Partial remission (PR) patients without prior radiotherapy or residual bone marrow involvement will receive Treatment 6 (radiotherapy). PR patients with prior radiotherapy or those with residual bone marrow involvement will receive Treatment 7 (4 additional cycles of MOP-BAP; after 10 total cycles of MOP-BAP, patient will continue study on MOPBAP therapy at the discretion of the investigator).

#### PROGRESS

Two patients were entered at MAMC in FY 84. One patient had a partial remission after three courses of MOPP-BAP and then was killed in a car accident. The other patient had a partial response and is now receiving radiotherapy.

STATUS: (O)

TITLE: SWOG 7823/24/25/26: ROAD-AdOAP in Acute Leukemia,  
Phase III

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC James E. Congdon, MC  
LTC Irwin B. Dabe, MC

WORK UNIT NO: 79/02

#### TECHNICAL OBJECTIVE

To compare the efficacy of the 4-drug combination chemotherapy regimen, ROAP (Rubidazone, Vincristine, Arabinosyl Cytosine, and Prednisone) to AdOAP (the same combination using Adriamycin in place of Rubidazone) in adult acute leukemia, as determined by remission duration and survival; to determine the comparative toxicity of these regimens; to determine whether late intensification therapy at 9 months after complete remission will improve long-term, disease free survival; to determine whether immunotherapy using Levamisole for 6 months after 12 months of complete remission on chemotherapy improves disease-free survival; to determine the effects of intrathecal Ara-C on the incidence of CNS leukemia; to determine reproducibility of the FAB/histologic classification and correlation to response to therapy in 200 consecutive cases of acute leukemia; and to study the effects of intensive supportive care in the management of acute leukemia.

#### METHOD

For remission induction, Group A will receive ROAP and Group B will receive AdOAP. When leukemic cells are no longer visible in the bone marrow, consolidation therapy will begin with one-half the patients receiving RAOP in reduced dosage. The other one-half will receive AdOAP with the addition of cytosine arabinoside in the spinal fluid at weekly intervals for 8 weeks. If a complete remission persists, maintenance therapy will be given consisting of vincristine, cytosine arabinoside, and prednisone for 5 days at monthly intervals for 9 months. One half of these patients will then receive late intensification therapy consisting of a combination of vincristine, prednisone, and methotrexate plus 6-mercaptopurine for 5 days. The other one-half will receive 3 additional months of maintenance therapy, at which time all patients will be randomized into one group receiving no further treatment and another group receiving levamisole for 2 days of each week for 6 months.

#### PROGRESS

(4/79 - 9/84) No new entries at MAMC during FY 84. Five patients were entered in previous years. Three expired from disease and two were lost to follow-up.

STATUS: (C)



TITLE: SWOG 7827: Combined Modality Therapy for Breast Carcinoma,  
Phase III

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC James E. Congdon, MC  
LTC Irwin B. Dabe, MC

WORK UNIT NO: 79/96

#### TECHNICAL OBJECTIVE

To compare the disease-free interval and recurrence rates in:  
(1) estrogen receptor positive premenopausal patients with Stage II disease using combination chemotherapy alone vs combination chemotherapy and oophorectomy; (2) estrogen receptor positive postmenopausal patients with Stage II disease using combination chemotherapy plus tamoxifen vs tamoxifen alone vs combination chemotherapy alone; (3) estrogen receptor negative patients with Stage II disease using one vs two years of combination chemotherapy; and to compare the effect of the various adjunctive therapy programs upon survival patterns and to correlate the estrogen receptor status with disease-free interval and survival.

#### METHOD

Patients with a histologically proven diagnosis of breast cancer (Stage II or Stage III) with one or more pathologically involved axillary nodes will receive one of the following treatments: (CMFVP = cyclophosphamide, methotrexate, 5-fluorouracil, vincristine, and prednisone):

- (1) CMFVP for 1 yr - pre or postmenopausal ER- patients.
- (2) CMFVP for 2 yr - pre or postmenopausal ER- patients.
- (3) CMFVP for 1 yr - premenopausal ER+ patients.
- (4) Oophorectomy + CMFVP - premenopausal ER+ patients.
- (5) Tamoxifen alone for 1 yr - postmenopausal ER+ patients.
- (6) CMFVP for 1 yr - postmenopausal ER+ patients.
- (7) Tamoxifen + CMFVP for 1 yr - postmenopausal ER+ patients.

Patients undergoing segmental mastectomy (lumpectomy) will receive 6 wks of radiation therapy in addition to the treatment they are randomized to receive.

#### PROGRESS

Eight new patients were entered in FY 84 for a total of 24 entries. Of the eight new patients, five have had no recurrence on protocol, one had chest wall recurrence during adjuvant therapy, and one had a recurrence on Tamoxifen and is now off study and receiving other chemotherapy.

STATUS: (0)

TITLE: SWOG 7916: Phase II Evaluation of Gallium Nitrate in  
Metastatic Urological Malignancies: Testicular, Bladder,  
Prostate, and Kidney

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC James E. Congdon, MC  
LTC Irwin B. Dabe, MC

WORK UNIT NO: 80/23

#### TECHNICAL OBJECTIVES

To determine the efficacy of gallium nitrate as determined by response and survival in patients with metastatic urological malignancies which include: testicular, bladder, prostate, and kidney; who have failed on higher priority treatment.

#### METHOD

Patients are eligible who are not candidates for studies of higher priority and who have histologically proven incurable advanced metastatic testicular carcinoma, bladder carcinoma, prostate or kidney carcinoma. Patients should not have had more than two previous types of combination or single agent chemotherapy trials.

All patients will be treated at a dose of 700 mg/m<sup>2</sup> given as a 30 minute IV infusion in 200 ml of normal saline. Course will be repeated every two weeks if blood counts, and liver and renal functions permit. An adequate trial will consist of two courses of therapy.

#### PROGRESS

(2/80 - 9/84) No entries at MAMC.

STATUS: (C)

TITLE: SWOG 7984: The Treatment of Chronic Stage CML with  
Pulse, Intermittent Busulfan Therapy with or without  
Oral Vitamin-A, Phase III

PRINCIPAL INVESTIGATOR: LTC Irwin B. Dabe, MC

PROFESSIONAL ASSISTANTS: COL F. H. Stutz, MC  
MAJ Lauren K. Colman, MC

WORK UNIT NO: 81/80

#### TECHNICAL OBJECTIVES

To determine the efficacy of standard pulse, intermittent busulfan therapy plus oral vitamin A in prolonging the chronic phase of CML, and hence in prolonging survival.

#### METHOD

Patients with a diagnosis of chronic stage CML for one year or less with no prior therapy are eligible. Patients will be stratified into those who had a splenectomy and those who did not. Randomization will be to busulfan alone or busulfan plus oral vitamin A. Stratification is also by age, <20 or >20 years. Treatment will continue for as long as the patient responds to the treatment and does not have unacceptable toxicity.

#### PROGRESS

No entries at MAMC.

STATUS: (0)

TITLE: SWOG 7990: Intergroup Testicular Study

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC James E. Congdon, MC  
LTC Irwin Dabe, MC

WORK UNIT NO: 80/33

#### TECHNICAL OBJECTIVES

To compare the disease-free survival and overall survival for surgery alone (with chemotherapy for relapsers) vs surgery plus early adjuvant chemotherapy in patients with resectable Stage II testicular cancer; to register and follow patients with nonseminoma, nonchoriocarcinoma Stage I testicular cancer to define prognostic variables which may predict recurrence in this stage group; to define the difference in disease-free rates and patterns of recurrence, based upon histologic subtypes and extent of disease on initial presentation; to evaluate the role of marker substances such as HCG, alpha-fetoprotein, and lactic dehydrogenase in the early detection and management of recurrence in patients with Stage I and Stage II testicular carcinoma; to evaluate the accuracy of lymphangiograms, CAT scans, and ultrasound studies for staging of retroperitoneal nodal involvement.

#### METHOD

Patients with histologically confirmed carcinoma (not pure seminoma or choriocarcinoma) of the testis Stage I or Stage II who have had an orchiectomy will be eligible. Patients will undergo bipedal lymphangiogram with the intent of retroperitoneal node dissection. Serum markers will be obtained orchiectomy and must be obtained prior to lymphadenectomy and one to two weeks after. If at two weeks any marker is positive but falling, markers will be repeated at 3-4 weeks and the 4-week value must be normal or serial determinations must be declining with time at a rate predicted by the known serum halflife of the marker. Entry will be at 2-4 weeks postoperatively. Stage I patients will be followed routinely and tumor markers should be negative 4 weeks postop. Stage II unresectable patients are not eligible. Stage II resectable patients will be treated in two treatment groups. Group I: no adjuvant chemotherapy with monthly follow-up until recurrence. Group II: adjuvant chemotherapy with vinblastine, bleomycin, and cis-platinum. Stages I and II who were originally randomized to the follow-up group and Stage II relapsing after chemotherapy will be further treated with vinblastine, bleomycin, and cis-platinum. Patients in complete or partial remission or showing improvement after relapse induction will receive maintenance treatment with vinblastine, repeated every 4 weeks until complete remissions have received 104 weeks of therapy and partial remissions and improvements may continue indefinitely. All other patients will go off study.

#### PROGRESS

No entries at MAMC.

STATUS: (O)

TITLE: SWOG 8017: 5-FU, Adriamycin, Streptozotocin, and  
Cyclophosphamide (FAC-S) in the Treatment of Metastatic  
Carcinoid Tumors, Phase II

PRINCIPAL INVESTIGATOR: MAJ Alfred H. Chan, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC James E. Congdon, MC  
LTC Irwin B. Dabe, MC  
MAJ Lauren K. Colman, MC  
MAJ Howard Davidson, MC  
MAJ Thomas M. Baker, MC

WORK UNIT NO: 82/11

#### TECHNICAL OBJECTIVE

To determine whether combination chemotherapy employing 5-Fluorouracil, is effective in the management of metastatic carcinoid; to study the duration of survival of patients with metastatic carcinoid tumor treated with combination chemotherapy regimens; to provide further information concerning the response and/or survival of patients with metastatic carcinoid originating in different sites and having different metastatic patterns.

#### METHOD

All patients except those with cardiac disease will receive the combination of 5-FU, cyclophosphamide, adriamycin, and streptozotocin. Patients will be divided into good and poor risk groups with medication adjusted accordingly. Courses will be repeated at 28 day intervals as tolerated. Patients with carcinoid or other varieties of cardiac disease will not receive adriamycin. An adequate trial is considered two courses.

#### PROGRESS

(11/81 - 1/84) No new entries at MAMC In FY 84. One patient entered on study during FY 82 and expired after failing to respond after two courses of treatment.

STATUS: (C)

TITLE: SWOG 8025: Combination Chemotherapy for Chronic Lymphocytic Leukemia, Phase II

PRINCIPAL INVESTIGATOR: LTC Irwin B. Dabe, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
MAJ Lauren K. Colman, MC

WORK UNIT: 81/81

#### TECHNICAL OBJECTIVES

To determine the response rate and duration of remission in patients with CLL treated with combination chemotherapy consisting of prednisone, vincristine, cytosine arabinoside, lytxan, and adriamycin; to correlate parameters obtained in the clinical, pathological, and immunological staging with response to treatment; to determine the effect of stopping chemotherapy after patients have achieved a complete remission plus 2 consolidation courses, in order to define a cured or stabilized fraction of patients.

#### METHOD

Patients with chronic lymphocytic leukemia fulfilling the criteria as outlined by the Rai classification of CLL (all stages) are eligible for this protocol. Patients who have been treated previously with a single alkylating agent are eligible but will be analyzed separately. Patients may not have received prior adriamycin or Ara-C; however, patients previously treated with radiation therapy alone are eligible, and these patients will also be analyzed separately. The protocol consists of Arm I which is applicable to Rai Classification, stages 1 and 2, which is registration only (no treatment) with careful documentation of the progression of the disease; and Arm II, Rai Classification 3-4, consisting of chemotherapy with a combination of prednisone, Oncovin, Ara-C, cyclophosphamide, and hydroxyduranubicin (adriamycin). Treatment will continue for as long as the patient responds on Arm II. Patients on Arm I at the time of progression to stage 3 or 4 will be eligible for treatment on the same combination chemotherapy regimen. Patients will be followed indefinitely or until death.

#### PROGRESS

5/81 - 12/83) No patients registered on protocol at MAMC. Additionally, accrual has been slow with a significant morbidity and mortality rate associated with the therapy.

STATUS: (C)

TITLE: SWOG 8030: Evaluation of DHAD in Advanced Squamous Cell Carcinoma of the Head and Neck, Phase II

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC Archie W. Brown, MC  
LTC Irwin B. Dabe, MC

WORK UNIT: 81/46

#### TECHNICAL OBJECTIVES

To determine the response rate and remission duration in patients with advanced squamous cell carcinoma of the head and neck treated with DHAD used in a single dose every-three-week schedule; to define further the qualitative and quantitative toxicities of DHAD.

#### METHOD

Patients with histologically confirmed diagnosis of squamous cell carcinoma of the neck or adenoid cystic carcinoma of the head and neck with measurable disease are eligible if they have become resistant to standard chemotherapy. Only patients with advanced disease not amenable to surgery or radiation are eligible. All patients must have measurable disease and have recovered from toxicities of previous therapies. Patients will be stratified according to prior chemotherapy or no prior chemotherapy and then will be treated with DHAD without randomization (12 mg/M<sup>2</sup> IV infusion in 100 cc D5W over 30 minutes, repeated every three weeks). Treatment will continue for as long as the tumor remains stable or shrinks. Treatment will be discontinued if the tumor progresses, if intolerable side effects occur, or if the patient refuses further treatment.

#### PROGRESS

(2/81 - 7/84) No patients registered on this protocol at MAMC.

STATUS: (C)

LE: SWOG 8037: Combined Therapies for Squamous Cell Cancer  
of the Esophagus, Phase II

NCIPAL INVESTIGATOR: MAJ Howard Davidson, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC James E. Congdon, MC  
LTC Irwin B. Dabe, MC  
MAJ Alfred H. Chan, MC  
MAJ Timothy J. O'Rourke, MC  
MAJ Thomas M. Baker, MC

UNIT NO: 82/69

#### TECHNICAL OBJECTIVE

determine the feasibility and toxicity of combined radiotherapy chemotherapy with 5-fluorouracil (5-FU) and cis-platinum followed by surgery in patients with epidermoid carcinoma of the middle or distal esophagus; to determine the time to local or distant progression in patients treated by these three combined modalities; to determine the survival of patients treated by these three combined modalities; and to determine the response rate by clinical and pathological staging at the time of surgery.

#### METHOD

For metastatic survey testing to determine that the patient has localized disease, the patient will be started on a simultaneous combination of chemotherapy and radiotherapy. The chemotherapy will consist of cis-platinum given through the side tubing of a newly running IV line over 2 hours followed by 5-FU given through a newly running IV by continuous infusion for 4 days. The patient will then be given a 4-week rest period and a similar chemotherapy regimen will be repeated. The exact dose of each chemotherapy agent will be determined by the patient's height and body weight. Simultaneous with the start of the chemotherapy, the patient will receive external beam radiation therapy to the esophagus in the region of the tumor. Approximately 2 weeks after the completion of the radiation and two courses of chemotherapy, the patient will be taken to surgery for definitive resection of the tumor. This will be followed by an anastomosis of the proximal remaining esophagus to the stomach.

#### PROGRESS

82 - 1/84) Principal investigator changed to MAJ Davidson in October 1983 from LTC Congdon. No patients registered on this protocol at MAMC.

TUS: (C)



TITLE: SWOG 8038: Vinblastine in Advanced Ovarian Cancer,  
Phase II

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: COL Roger B. Lee, MC  
LTC Irwin B. Dabe, MC

DRK UNIT: 81/72

#### TECHNICAL OBJECTIVES

to determine the response rate and remission duration with intravenous therapy using Velban as a continuous infusion in patients with advanced ovarian cancer; to define further the qualitative and quantitative toxicity of the continuous infusion of Velban.

#### METHOD

This is a Phase II study using vinblastine infusion. Patients with extensive epithelial ovarian tumors with measurable disease are eligible. Patients must meet other criteria as outlined in the protocol. The Velban will be administered as a continuous 5-day infusion once every three weeks. This will be continued as long as the tumor remains stable or shrinks. Treatment will be discontinued for patient refusal of further treatment or intolerable toxicity. Patients will be stratified according to bilirubin, SGOT, and alkaline phosphatase status.

#### PROGRESS

4/81 - 12/83) No new entries in FY 84. One patient registered FY 82) with stable disease for two months and later expired. Patient had mild nausea, vomiting, and severe neutropenia.

STATUS: (C)

: SWOG 8040: Evaluation of Combination Chemotherapy (FAM-S)  
vs a Phase II Drug in Pancreatic Adenocarcinoma, Phase II

IPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

SSIONAL ASSISTANTS: LTC Irwin B. Dabe, MC  
MAJ Lauren K. Colman, MC

JNIT: 81/84

#### TECHNICAL OBJECTIVES

determine the response rate and survival in patients with  
advanced pancreatic adenocarcinoma treated with 5-FU, Adriamycin,  
cytosine arabinoside (Ara-C), and Streptozotocin (FAM-S); to determine further  
toxicity of the FAM-S regimen; to determine the activity of  
the Phase II drug in previously untreated patients with advanced  
carcinoma of the pancreas by determination of response  
and duration of response and survival; to determine further  
toxicity of each Phase II agent.

#### METHOD

Patients with histologically confirmed adenocarcinoma of the  
pancreas with distant metastasis (liver, peritoneum)  
whose disease is localized and not amenable to curative surgery  
and who have not received prior chemotherapy  
are eligible. All patients must have objectively  
measurable disease and have not received any prior chemotherapy  
or radiation therapy. Patients must also meet other criteria as  
outlined in the protocol. Patients will be stratified according  
to whether a biopsy only performed vs. palliative bypass procedures and  
performance status. Subsequently, the patient will be randomized  
to either a combination chemotherapy regimen consisting of 5-FU,  
adriamycin, mitomycin, and streptozotocin or a Phase II agent.  
The Phase II agent will be changed periodically when sufficient patients are  
enrolled on one arm. If the patient fails or has a response  
and subsequently has increasing disease, a cross-over is recom-  
mended. Patients on FAM-S will cross over to the Phase II agent  
vice versa. Chemotherapy will continue for as long as the  
disease remains stable or the tumor is shrinking. Progressive  
disease, patient refusal of further treatment, or intolerable  
side effects are criteria for discontinuation of the protocol.

#### PROGRESS

- 3/84) No new entries in FY 84. One patient was  
enrolled in FY 83. This patient received only one treatment  
which had no effect on the progression of her disease.  
She refused any further chemotherapy and later expired.

Signature: (C)

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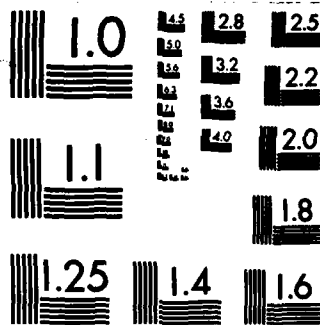
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## Future



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TITLE: SWOG 8043: Evaluation of DHAD in Pancreatic Adenocarcinoma,  
Phase II

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: LTC Irwin B. Dabe, MC  
MAJ Lauren K. Colman, MC

WORK UNIT: 81/86

#### TECHNICAL OBJECTIVES

To determine the antitumor activity of DHAD, as determined by response rate and duration of response, used in a single dose schedule every three weeks in patients with advanced adenocarcinoma of the pancreas; to determine additional information concerning the nature and degree of toxicity of this drug.

#### METHOD

This protocol is an adjunct to SWOG 8040. In this protocol, MGBG is the Phase II Agent set forth in the master protocol; therefore, the methods of the protocol will be the same as for SWOG 80/40.

#### PROGRESS

(5/81 - 9/84) No new entries in FY 84. One patient was entered in FY 82 with stable disease for five months while on treatment. Severe neutropenia was noted as a side effect.

STATUS: (C)

TITLE: SWOG 8044: Evaluation of AZQ in Pancreatic Carcinoma,  
Phase II

PRINCIPAL INVESTIGATOR: MAJ Howard Davidson, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC Irwin B. Dabe, MC  
MAJ Thomas M. Baker, MC  
MAJ Alfred H. Chan, MC  
MAJ Timothy J. O'Rourke, MC  
CPT Michael D. Stone, MC

WORK UNIT NO: 84/17

#### TECHNICAL OBJECTIVES

To determine the antitumor activity of AZQ (NSC-182986) in pancreatic carcinoma and to further determine the nature and extent of AZQ toxicity in a Phase II study.

#### METHOD

This protocol is an adjunct to SWOG 8040. In this protocol, AZQ is the Phase II agent set forth in the master protocol; therefore, the methods of the protocol will be the same as for SWOG 80/40. These patients will be closely followed and at the first sign of disease progression, will be crossed over to receive the FAM-S.

#### PROGRESS

(11/83 - 9/84) No entries at MAMC. As of Sept 1984, 37 patients had been entered throughout SWOG. No toxicity or response data are available.

STATUS: (C)

TITLE: SWOG 8049: Treatment of Resected, Poor Prognosis  
Malignant Melanoma: Stage I: Surgical Excision vs  
Surgical Excision + Vitamin A

PRINCIPAL INVESTIGATOR: MAJ Howard Davidson, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC James E. Congdon, MC  
LTC Irwin B. Dabe, MC  
MAJ Thomas M. Baker, MC  
MAJ Alfred H. Chan, MC  
MAJ Lauren K. Colman, MC

WORK UNIT NO: 82/13

#### TECHNICAL OBJECTIVE

To determine the efficacy of surgical excision or surgical excision plus vitamin A in preventing the recurrence of high risk, Stage I malignant melanoma by determination of remission or disease-free interval; to determine the immunocompetence of patients with malignant melanoma and to determine the influence of vitamin A upon that immunocompetence.

#### METHOD

Patients will be equally randomized between the two treatment arms: vitamin A versus no further treatment. Patients will be stratified by depth of invasion, sex, and type of surgery. Those patients randomized to receive vitamin A will receive a dose of 100,000 I.U. daily. Treatment will continue for 18 months. Patients who receive no treatment will be followed until relapse and removal from the study.

#### PROGRESS

No new entries in FY 84. Groupwide, 185 patients have been entered. Headache occurs in 8% of the vitamin A treated patients; overall toxicity is minimal.

STATUS: (O)

**TITLE:** SWOG 8092: Use of Human Tumor Cloning System to Select Chemotherapy for Patients with Ovarian Cancer Refractory to Primary Therapy

**PRINCIPAL INVESTIGATOR:** COL Friedrich H. Stutz, MC

**PROFESSIONAL ASSISTANTS:** COL Roger B. Lee, MC  
LTC Irwin B. Dabe, MC

**WORK UNIT NO:** 81/87

#### TECHNICAL OBJECTIVES

To utilize the human tumor cloning assay to select single agent chemotherapy for patients with epithelial-type ovarian cancer, refractory to standard therapy; to determine if the human tumor cloning system can be utilized to select the therapy of individual patients in a cooperative group setting.

#### METHOD

Patients with a pathologic diagnosis of epithelial-type ovarian cancer in pleural or peritoneal fluid or with solid tumor are eligible to have specimens sent to tumor cloning laboratories. These specimens will be cultured and incubated with antineoplastic agents to determine their sensitivity to these chemotherapeutic agents. In ovarian cancer resistant to standard treatment, treatment recommendations will be made. All these patients should have measurable disease. Other tumor specimens will be tested; however, no treatment recommendations will be made in these instances, especially when the patient was previously untreated with chemotherapy. This is an ancillary study and involves treatment only in patients with epithelial type ovarian cancer. This treatment continues for as long as the patient responds, tolerates the treatment, and continues to accept the investigational treatment.

#### PROGRESS

(5/81 - 9/84) No new entries at MAMC in FY 84. Two patients entered; one in FY 81, the other in FY 82. There was no growth from either patient's tumor. Both patients have expired since that time.

**STATUS:** (C)



**TITLE: SWOG 8107: Management of Disseminated Melanoma,  
Master Protocol, Phase II-III.**

**PRINCIPAL INVESTIGATOR: MAJ Howard Davidson, MC**

**PROFESSIONAL ASSISTANTS: COL F. H. Stutz, MC  
LTC James E. Congdon, MC  
LTC Irwin B. Dabe, MC  
MAJ Thomas M. Baker, MC  
MAJ Alfred H. Chan, MC  
MAJ Timothy J. O'Rourke, MC**

**WORK UNIT NO: 83/05**

#### TECHNICAL OBJECTIVE

To determine the effectiveness of cranial irradiation given electively in disseminated melanoma patients with lung and/or liver metastasis to prevent or delay the clinical appearance of brain metastasis and to determine the efficacy of high intermittent doses of cis-platinum with the use of IV hydration and mannitol diuresis in patients with advanced malignant melanoma refractory to higher priority protocols.

#### METHOD

This protocol employs some of the newer kinetic concepts of chemotherapy and radiation therapy. Patients will be randomized to receive 3000 rads of prophylactic whole brain radiation therapy versus close observation for the development of brain metastasis. Second randomization will be to one of three chemotherapy arms:

ARM 1 - DTIC and Actinomycin D.  
ARM 2 - Cis-platinum, Velban and Bleomycin  
ARM 3 - Cis-platinum

All chemotherapy agents will be given intravenously once every three weeks. Should there be objective evidence of disease progression during the course of the study, the patient will be crossed over to a treatment arm composed of drugs not used in the first treatment arm.

#### PROGRESS

(82 10 - 83 09) Two patients were entered in FY 84 with no unexpected toxicities. Groupwide toxicities were largely those expected. No fatalities due to toxicity but some life threatening neutropenia and thrombocytopenia in arm receiving DTIC and actinomycin. In patients evaluable thus far, no complete responses. Partial response rates ranging 0 to 30%.

**STATUS: (0)**

TITLE: SWOG 8116: Evaluation of Bisantrane Hydrochloride in  
Refractory Lymphoma, Phase II

PRINCIPAL INVESTIGATOR: MAJ Howard Davidson, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC James E. Congdon, MC  
LTC Irwin B. Dabe, MC  
MAJ Thomas M. Baker, MC  
MAJ Alfred H. Chan, MC  
MAJ Lauren K. Colman, MC

WORK UNIT NO: 82/48

#### TECHNICAL OBJECTIVE

To determine the response rate and response duration of malignant lymphoma treated with bisantrene hydrochloride used in a single dose, every-three-week schedule; to define the qualitative and quantitative toxicities of bisantrene administered in a Phase II study.

#### METHOD

This is a Phase II clinical trial of a new chemotherapy agent, bisantrene hydrochloride used in patients with malignant lymphomas of the Hodgkin's and non-Hodgkin's varieties that have not responded to standard treatment modalities. The drug has demonstrated some effectiveness in controlling lymphomas in a variety of laboratory animals. It has been tested in Phase I trials in humans, and its toxicities, including temporary bone marrow suppression, nausea, emesis, alopecia, transient hypotension, and pain at the injection site have been recognized. All patients in this study will have met a number of performance and laboratory eligibility criteria as listed in the protocol. Bisantrane hydrochloride will be administered through the side tubing of a freely flowing IV line in an amount determined by the patient's body surface area. The treatments will be repeated at three week intervals, unless unusual toxicities are encountered, for a minimum of two courses or until objective evidence of disease progression is ascertained.

#### PROGRESS

(5/82 - 3/84) No patients registered on the protocol at MAMC.

STATUS: (C)

TITLE: SWOG 8117: Evaluation of Bisantrane Hydrochloride in Refractory Ovarian Cancer, Phase II

PRINCIPAL INVESTIGATOR: MAJ Howard Davidson, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC James E. Congdon, MC  
LTC Irwin B. Dabe, MC  
MAJ Thomas M. Baker, MC  
MAJ Alfred H. Chan, MC  
MAJ Lauren K. Colman, MC

WORK UNIT NO: 82/49

#### TECHNICAL OBJECTIVE

To determine the response rate and response duration of refractory ovarian cancer treated with bisantrene hydrochloride used in a single dose, every-three-week schedule; to define the qualitative and quantitative toxicities of bisantrene administered in a Phase II study.

#### METHOD

This is a Phase II clinical trial evaluating a new chemotherapy agent, bisantrene hydrochloride, in the treatment of refractory ovarian carcinoma. Bisantrane is one of a series of new synthetic anticancer drugs in the hydrazone class which have demonstrated some in vitro activity in cell culture work against ovarian carcinoma as well as some in vivo efficacy in human volunteers. The clinical toxicities have been delineated in Phase I trials and include transient myelo suppression, nausea, emesis, transient alopecia, transient mild hypotension, and local superficial ulceration of the skin with extravasation of the drug at the IV site. The exact dosage of bisantrene that the patient will receive depends on several factors including the patient's height, body weight, and performance standards on several laboratory tests which evaluate bone marrow, hepatic, and renal function. The drug will be administered, dissolved in 500 cc of dextrose in water solution, through a freely flowing IV line over two hours. Unless unusual toxicities are encountered, the treatments will be repeated at three week intervals, for a minimum of two cycles or until objective evidence of disease progression is ascertained.

#### PROGRESS

(5/82 - 12/83) No new entries at MAMC in FY 84. One patient was entered but not started on the drug because of rapidly worsening complications of disease.

STATUS: (C)

**TITLE:** SWOG 8118: Evaluation of Bisantrane Hydrochloride in Refractory Malignant Melanoma, Phase II

**PRINCIPAL INVESTIGATOR:** MAJ Howard Davidson, MC

**PROFESSIONAL ASSISTANTS:** COL Friedrich H. Stutz, MC  
LTC James E. Congdon, MC  
LTC Irwin B. Dabe, MC  
MAJ Thomas M. Baker, MC  
MAJ Alfred H. Chan, MC  
MAJ Lauren K. Colman, MC

**WORK UNIT NO:** 82/50

#### TECHNICAL OBJECTIVE

To determine the response rate and response duration of malignant melanoma treated with bisantrene hydrochloride used in a single dose, every-three-week schedule; to define the qualitative and quantitative toxicities of bisantrene administered in a Phase II study.

#### METHOD

This is a Phase II clinical trial evaluating a new chemotherapy agent, bisantrene hydrochloride, in the treatment of malignant melanoma which has become refractory to standard treatment modalities. This drug has demonstrated some effectiveness in controlling malignant melanoma neoplasms in cell cultures and in a variety of laboratory animals. The drug has been tested in Phase I clinical trials in human beings and its toxicities, including temporary bone marrow suppression, nausea, emesis, alopecia, mild hypotension, and pain at the injection site, have been recognized. All patients entered into the study will have met a number of performance and laboratory eligibility criteria as outlined in the protocol. Bisantrane hydrochloride will be administered through the side tubing of a freely flowing IV line in an amount determined by the patient's body surface area. Unless unusual toxicities are encountered, the treatments will be repeated at three week intervals, for a minimum of two cycles or until objective evidence of disease progression is ascertained.

#### PROGRESS

(5/82 - 9/84) No patients registered on the protocol at MAMC.

**STATUS:** (C)

TITLE: SWOG 8119: Evaluation of Bisantrane Hydrochloride in  
Hepatoma, Phase II

PRINCIPAL INVESTIGATOR: MAJ Howard Davidson, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC James E. Congdon, MC  
LTC Irwin B. Dabe, MC  
MAJ Thomas M. Baker, MC  
MAJ Alfred H. Chan, MC  
MAJ Lauren K. Colman, MC

WORK UNIT NO: 82/51

#### TECHNICAL OBJECTIVE

To determine the response rate and response duration of hepatomas treated with bisantrene hydrochloride used in a single dose, every-three-week schedule; to define the qualitative and quantitative toxicities of bisantrene administered in a Phase II study.

#### METHOD

This is a Phase II clinical trial evaluating a new chemotherapy agent, bisantrene hydrochloride, in the treatment of malignant primary carcinoma of the liver. The patients will have all failed on prior standard treatments including surgery, radiation therapy, and chemotherapy. This drug has demonstrated some effectiveness in controlling primary liver cancer in a variety of laboratory animals. The drug has been tested in Phase I clinical trials in human beings and its toxicities, including temporary nausea, emesis, alopecia, transient mild hypotension, transient mild myelosuppression, and localized pain at the injection site, have been recognized. All patients entered into the study will have met a number of performance and laboratory eligibility criteria as outlined in the protocol. Bisantrane hydrochloride will be administered through the side tubing of a freely flowing IV line in an amount determined by the patient's body surface area. Unless unusual toxicities are encountered, the treatments will be repeated at three week intervals, for a minimum of two cycles or until objective evidence of disease progression is ascertained.

#### PROGRESS

No patients registered on the protocol at MAMC.

STATUS: (O)

TITLE: SWOG 8120: Evaluation of Bisantrone Hydrochloride in  
Gastric Carcinoma, Phase II

PRINCIPAL INVESTIGATOR: MAJ Howard Davidson, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC James E. Congdon, MC  
LTC Irwin B. Dabe, MC  
MAJ Thomas M. Baker, MC  
MAJ Alfred H. Chan, MC  
MAJ Lauren K. Colman, MC

WORK UNIT NO: 82/52

#### TECHNICAL OBJECTIVE

To determine the response rate, response duration, and survival of gastric carcinoma treated with bisantrene hydrochloride used in a single dose, every-three-week schedule; to define the qualitative and quantitative toxicities of bisantrene administered

#### METHOD

This is a Phase II clinical trial evaluating a new chemotherapy agent, bisantrene hydrochloride, in the treatment of malignant primary gastric carcinoma. The patients will have all failed on prior standard treatments including surgery and standard chemotherapy agents. This drug has demonstrated some effectiveness in controlling the growth of primary gastric carcinomas in cell culture work and moderate effectiveness in several laboratory animals. The drug has been tested in Phase I clinical trials in human beings and its toxicities, including temporary nausea, emesis, alopecia, transient mild hypotension, transient mild myelosuppression, and localized pain at the injection site, have been recognized. All patients entered into the study will have met a number of performance and laboratory eligibility criteria as outlined in the protocol. Bisantrone hydrochloride will be administered through the side tubing of a freely flowing IV line in an amount determined by the patient's body surface area as well as the patient's overall performance status. Unless unusual toxicities are encountered, the treatments will be repeated at three week intervals, for a minimum of two cycles or until objective evidence of disease progression is ascertained.

#### PROGRESS

(5/82 - 10/83) No new entries at MAMC in FY 84. One patient was entered in FY 83. Groupwise, 17 patients were entered. No life threatening toxicities were reported.

STATUS: (C)

TITLE: SWOG 8203/04: Randomized Comparison of Adriamycin, Mitoxantrone, and Bisantrone in Patients with Metastatic Breast Cancer Not Previously Exposed to Intercalating Chemotherapy, Phase III

PRINCIPAL INVESTIGATOR: MAJ Howard Davidson, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC James E. Congdon, MC  
LTC Irwin B. Dabe, MC  
MAJ Thomas M. Baker, MC  
MAJ Alfred H. Chan, MC  
MAJ Timothy J. O'Rourke, MC

WORK UNIT NO: 83/13

#### TECHNICAL OBJECTIVES

To determine the comparative response rate, duration of response, and survival of equimyelosuppressive doses of Adriamycin, Mitoxantrone, and Bisantrone as single agents in breast cancer patients, not previously exposed to an intercalating agent, using a single dose, every-three-week schedule; to determine the salvage response rate of these agents in breast cancer patients failing one of these three agents; to assess the cardiotoxicity of these agents as determined by history, physical examination, and measurement of the left ventricular ejection fraction; to compare the relative noncardiac toxicities of these agents; to prospectively evaluate the *in vitro* effects of these drugs in the cloning assay and correlate them with *in vivo* activity in those patients with biopsiable disease; and to measure the peak plasma levels of each drug and correlate the levels with response and toxicity.

#### METHOD

Patients will be randomized to receive equivalent doses of either Adriamycin, Metoxantrone or Bisantrone intravenously once every 3 weeks as an out patient. The medicine will be continued until evidence of disease progression is noted or until maximum allowed dose of Adriamycin is achieved. Frequent studies including blood tests, x-rays and nuclear medicine scans will be performed on these patients in order to determine response to the treatment and spot early toxicities. At the first sign of documented disease progression, the patient will be re-randomized to receive one of the two other agents.

#### PROGRESS

(11/82 - 5/84) This study was closed to MAMC by the national group because the number of patients accrued had been too low. No patients were entered in FY 84.

STATUS: (T)

TITLE: SWOG 8207: AZQ in Advanced Renal Cell Carcinoma,  
Phase II

PRINCIPAL INVESTIGATOR: MAJ Howard Davidson, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC James E. Congdon, MC  
LTC Irwin B. Dabe, MC  
MAJ Thomas M. Baker, MC  
MAJ Alfred H. Chan, MC  
MAJ Timothy J. O'Rourke, MC

WORK UNIT NO: 82/71

#### TECHNICAL OBJECTIVE

To determine the response rate and duration of response in patients with advanced renal cell carcinoma treated with AZQ (aziridinylbenzoquinone) used in a single dose, every-three-week schedule; and to define the qualitative and quantitative toxicities of AZQ administered in a phase II study.

#### METHOD

This is a phase II study designed to determine the efficacy of a new agent, AZQ, in the treatment of advanced renal cell carcinoma. It has shown promising in vitro and in vivo efficacy in a number of adenocarcinomas including renal cell carcinoma. The drug will be given through the side tubing of a freely running IV every 3 weeks (good risk: 40 mg/M<sup>2</sup>, poor risk: 30 mg/M<sup>2</sup>). The treatments will be continued on a 3-week basis as long as there is objective evidence of disease stabilization or regressions. Treatment will be terminated if unacceptable side effects develop or if there is objective evidence of disease progression.

#### PROGRESS

(9/82 - 3/84) No patients registered at MAMC. In other institutions severe granulocytopenia and life-threatening thrombocytopenia were observed. This protocol was temporarily closed and then reopened in an amended form because of these complications.

STATUS: (C)



TITLE: SWOG 8241: Treatment for Advanced Non-Small Cell Lung Cancer: PVp Versus PVpM Versus PVE Versus PVeMi Versus FOMi/CAP, Phase III

PRINCIPAL INVESTIGATOR: MAJ Howard Davidson, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC James E. Congdon, MC  
LTC Irwin B. Dabe, MC  
MAJ Thomas M. Baker, MC  
MAJ Alfred H. Chan, MC  
MAJ Timothy J. O'Rourke, MC

WORK UNIT NO: 83/46

#### TECHNICAL OBJECTIVES

To directly compare the efficacy and toxicity of cis-platinum plus VP-16 (PVp) versus cis-platinum plus vinblastine (PVe) in patients with advanced non-small cell lung cancer; to compare the response rate, response duration, survival, and toxicity of PVp to cis-platinum plus VP-16 plus MGBM (PVpM); to compare the response rate, response duration, survival and toxicity of PVe to cis-platinum plus Vinblastine plus Mitomycin-C (PVeMi); to re-evaluate and compare the activity of FOMi/CAP to PVp, PVpM, PVe and PVeMi using a five arm, randomized study design; to evaluate differences in response rates among patients with squamous cell carcinoma, adenocarcinoma or large cell undifferentiated carcinoma of the lung.

#### METHOD

After adequate laboratory tests to determine extent of disease, patients will be randomized to 1 of 5 treatment arms. ARM 1 consists of cis-platinum plus VP-16 every 4 weeks for 3 courses, then every 6 weeks thereafter. ARM 2 consists of cis-platinum plus VP-16 plus MGBG to be repeated at 4 weeks times 2 cycles and thereafter every 6 weeks. ARM 3 consists of cis-platinum and vinblastine to be repeated every 7 weeks. ARM 4 consists of cis-platinum plus mitomycin C to be repeated every 7 weeks. ARM 5 consists of 6 drugs on an alternating schedule, 5-flurouracil plus vincristine, plus mitomycin C will be alternated every 4 weeks with cyclophosphamide plus adriamycin, plus cis-platinum. These complete cycles will be repeated every 8 weeks. Treatment of all 5 ARMS may be discontinued after 12 months in patients achieving a complete remission status. The patients will be removed from the study at the first objective evidence of disease progression.

#### PROGRESS

(3/83 - 9/84) Four patients were entered at MAMC in FY 84 for a total of eight patients with no severe side effects. Groupwise, the preliminary conclusion is that all 5 arms of the study have equivalent response rates in the range of 20%. This is lower than expected on the basis of smaller single institution studies of the various regimens. Performance status was a significant predictor for chance of response.

STATUS: (C)

TITLE: SWOG 8237: Evaluation of Continuous Infusion Vinblastine Sulfate in Pancreatic Adenocarcinoma, Phase II

PRINCIPAL INVESTIGATOR: MAJ Thomas M. Baker, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC Irwin B. Dabe, MC  
MAJ Alfred H. Chan, MC  
MAJ Howard Davidson, MC  
MAJ Timothy J. O'Rourke, MC  
CPT Michael D. Stone, MC

WORK UNIT NO: 83/72

#### TECHNICAL OBJECTIVE

To determine the clinical response rate of a five-day continuous infusion of vinblastine sulfate in pancreatic adenocarcinoma.

#### METHOD

Patients will be treated with vinblastine sulfate at a starting dose of 1.4 mg/M<sup>2</sup>/day by continuous infusion for five days. Vinblastine sulfate will be repeated every three weeks provided granulocyte and platelet counts are satisfactory. If the counts do not recover until four weeks, the chemotherapy will be given on a four week cycle at the same dose. If the counts have not recovered within four weeks, vinblastine sulfate will be given at a one dose level of reduction when the counts have recovered. Therapy will be continued as long as there is stable disease, partial response, or complete response and acceptable clinical toxicity. An adequate trial will be defined as two cycles of continuous infusion vinblastine therapy.

#### PROGRESS

No entries at MAMC. Groupwide, 57% had mild or no toxicity, 43% had moderate leukopenia, thrombocytopenia, anemia, and toxicity.

STATUS: (O)

**TITLE:** SWOG 8232: Treatment of Limited Small Cell Lung Cancer with VP-16/Cis-Platinum Alternating with Vincristine/Adriamycin/Cyclophosphamide and Radiation Therapy versus Concurrent VP-16/Vincristine/Adriamycin/Cyclophosphamide and Radiation Therapy, Phase III

**PRINCIPAL INVESTIGATOR:** MAJ Howard Davidson, MC

**PROFESSIONAL ASSISTANTS:** COL Friedrich H. Stutz, MC  
LTC James E. Congdon, MC  
LTC Irwin B. Dabe, MC  
MAJ Thomas M. Baker, MC  
MAJ Alfred H. Chan, MC  
MAJ Timothy J. O'Rourke, MC

**WORK UNIT NO:** 83/45

#### TECHNICAL OBJECTIVES

To compare the efficacy of alternating non-cross-resistant, multidrug regimens with concurrent combination chemotherapy as remission induction in patients with limited small cell lung carcinoma and to determine the toxicity of these treatment programs.

#### METHOD

After appropriate laboratory tests to determine that the patient has limited disease, the patient will be randomized to one of two treatment arms: ARM 1 - includes 4 agents, VP-16, vincristine, adriamycin and cyclophosphamide. These agents will be given IV every 3 weeks for a total of 6 courses. ARM 2 - consists of VP-16 and cis-platinum alternating every 3 weeks with vincristine, adriamycin, and cyclophosphamide. These regimens will be repeated for a total of 6 treatments or 3 treatments of each group of drugs. At the end of 6 cycles of therapy, the patients will be restaged. For those patients with no evidence of disease remaining or those who have had a large decrease in the size of their tumor with only residual tumor remaining in the chest will receive radiation therapy to mediastinal and hilar regions and prophylactic whole brain radiation therapy. At the completion of this phase of treatment, the patients will receive 6 more cycles of the same chemotherapy regimen that they received prior to radiation therapy.

#### PROGRESS

Three patients were entered at MAMC in Fy 84. Groupwide, complete responses have been noted in 25% of Arm I patients and in 37% of Arm II patients. Median survival has been 55-60 weeks. Fatal granulocytopenia was noted in 2% of Arm I patients. Life-threatening or severe granulocytopenia was seen in 24% of Arm I patients and in 16% of Arm II patients.

**STATUS:** (O)

TITLE: SWOG 8231: Chemotherapy of Extragonadal Germinal Cell Neoplasms, Phase III

PRINCIPAL INVESTIGATOR: MAJ Howard Davidson, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC William Belville, MC  
LTC Irwin B. Dabe, MC  
MAJ Thomas M. Baker, MC  
MAJ Alfred H. Chan, MC  
MAJ Timothy J. O'Rourke, MC  
CPT Michael Stone, MC

WORK UNIT NO: 83/68

#### TECHNICAL OBJECTIVES

To determine the effectiveness of alternating combination chemotherapy consisting of VBP (vinblastine, bleomycin and cis-platinum) and EBAP (bleomycin, adriamycin, cis-platinum and VP-16) in patients with metastatic germinal cell neoplasms arising in extragonadal sites; to determine the overall toxicity of the alternating combination of VBP and EBAP; to determine the role of surgical removal of residual disease following this drug combination in partially responding patients; to compare the response rates observed in this study with those reported by other investigators.

#### METHOD

This study will utilize alternating combination chemotherapy, with first and third cycles consisting of VBP and the second and fourth cycles consisting of EBAP. There are reduced "poor risk" doses for patients who are over 65 or have neutropenia, thrombocytopenia, markedly abnormal liver function, or prior radiation therapy.

Following completion of the four cycles, those patients with a complete response will be observed; those with stable disease, minimal response, or partial response will have surgical resection of residual disease, if possible, followed by 2 more cycles of chemotherapy if malignant tumor is found at surgery.

#### PROGRESS

No entries at MAMC.

STATUS: (0)

SWOG 8229/30 - Davidson

therapy will receive Arm V (sequential half-body radiotherapy and concomitant vincristine and prednisone for six weeks).

#### PROGRESS

Two patients were entered at MAMC during FY 84. One patient was neutropenic at the start of treatment due to extensive disease and had neutropenic fever after first cycle. The other patient completed induction and then had upper hemibody radiation, but has since had eight months of thrombocytopenia precluding giving lower hemibody radiation.

Groupwide, 216 patients have been entered with no fatal toxicity, but 2% life-threatening thrombocytopenia and 2% life-threatening granulocytopenia were recorded.

STATUS: (0)

**TITLE:** SWOG 8229/30: Combined Modality Therapy for Multiple Myeloma, VMCP-VBAP for Remission Induction Therapy: VMCP + Levamisole vs Sequential Half-Body Radiotherapy + Vincristine-Prednisone for Patients Who Fail to Achieve Remission Status with Chemotherapy Alone, Phase III

**PRINCIPAL INVESTIGATOR:** MAJ Howard Davidson, MC

**PROFESSIONAL ASSISTANTS:** COL Friedrich H. Stutz, MC  
LTC James E. Congdon, MC  
LTC Irwin B. Dabe, MC  
MAJ Thomas M. Baker, MC  
MAJ Alfred H. Chan, MC  
MAJ Timothy J. O'Rourke, MC

**WORK UNIT NO:** 83/61

#### TECHNICAL OBJECTIVES

To compare the effectiveness of two intermittent pulse schedules of the chemotherapy combination of vincristine, melphalan, cyclophosphamide and prednisone (VMCP) + vincristine, BCNU, ardiamycin and prednisone (VBAP) (alternating versus syncopated) for induction of remission in previously untreated patients with multiple myeloma. Results will also be compared with other combination chemotherapy treatments in previous SWOG studies. In patients proven to achieve remission, to compare the value of 12 months of chemo-immunotherapy maintenance, VMCP + levamisole, versus a consolidation program consisting of sequential half-body radiotherapy along with vincristine and prednisone followed by unmaintained remission. In patients who only achieve improvement to determine whether sequential halfbody radiotherapy along with vincristine and prednisone will increase the remission rate. To determine whether sequential half-body radiotherapy along with vincristine and prednisone can serve as an effective form of induction therapy for patients who fail to respond to chemotherapy or suffer early relapse.

#### METHOD

Only patients with previously untreated multiple myeloma are eligible. Patients will be stratified as to tumor mass status and then randomized to induction therapy on Arm I (VMCP alternated every three weeks with VBAP for a minimum of 6 months to a maximum of one year) or Arm II (VMCP for 3 cycles followed by 3 cycles of VBAP. Each course will be repeated every 3 weeks. Courses will be repeated for a minimum of 6 months to a maximum of one year). Upon completion of induction, patients with documented 75% regression with chemotherapy alone will be randomized to receive Arm III (VMCP + levamisole, repeated every three weeks) or Arm IV (sequential half-body radiotherapy and concomitant vincristine and prednisone). Patients who are partial responders (50-75% regression) or non-responders (<50% or early relapse) following induction

**TITLE: SWOG 8228 - Correlation Between Progesterone Receptor and Response to Tamoxifen in Patients with Newly Diagnosed Breast Disease, Phase II**

**PRINCIPAL INVESTIGATOR: MAJ Howard Davidson, MC**

**PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC James E. Congdon, MC  
LTC Irwin B. Dabe, MC  
MAJ Thomas M. Baker, MC  
MAJ Alfred H. Chan, MC  
MAJ Timothy J. O'Rourke, MC**

**WORK UNIT NO: 83/55**

#### **TECHNICAL OBJECTIVE**

To determine the prognostic role of progesterone receptor in patients with newly diagnosed metastatic breast disease by correlating progesterone receptor levels with objective response rates in women treated with tamoxifen.

#### **METHOD**

ER+, non-pregnant female patients with new metastatic breast carcinoma are eligible. Patients who have received prior hormonal adjuvant therapy are eligible provided that they have not failed during therapy and the therapy has been stopped for at least three months. Patients with adjuvant chemotherapy alone are eligible. Patients with massive liver involvement are not eligible.

Tamoxifen, 10 mg po, twice daily, will be given alone until there is documented progression of the disease. Clear cut response may not be observed until 6-12 weeks of tamoxifen therapy. Therefore, therapy will not be discontinued unless there is evidence of disease progression at four weeks or unsatisfactory stable disease after eight weeks of therapy.

#### **PROGRESS**

No entries at MAMC. Eleven patients have been entered groupwide with hot flashes and occasional nausea as expected with tamoxifen.

**STATUS: (0)**

TITLE: SWOG 8221: Treatment of Advanced Bladder Cancer with Preoperative Irradiation and Radical Cystectomy Versus Radical Cystectomy Alone, Phase III

PRINCIPAL INVESTIGATOR: MAJ Howard Davidson, MC

PROFESSIONAL ASSISTANTS: COL Donald Kull, MC  
COL Friedrich H. Stutz, MC  
LTC William Belville, MC  
LTC Irwin B. Dabe, MC  
MAJ Thomas M. Baker, MC  
MAJ Alfred H. Chan, MC  
MAJ Timothy J. O'Rourke, MC  
CPT Michael Stone, MC

WORK UNIT NO: 84/19

#### TECHNICAL OBJECTIVE

To compare survival and pelvic recurrence rates in patients with transitional cell bladder cancer treated with radical surgery alone versus patients treated with preoperative irradiation with 2,000 rads followed by cystectomy.

#### METHOD

Patients eligible to be entered, must have histologically proven transitional cell carcinoma of the urinary bladder, and must have one of the following characteristics:

1. Evidence of muscle invasion.
2. Rapidly recurring superficial high-grade tumors and/or diffuse carcinoma *in situ* not amenable to TUR and/or intravesical chemotherapy.

Patients will be randomized to receive either surgery with radical cystectomy or radiation therapy plus radical cystectomy. Patients will be seen in follow-up every three months following the cystectomy. Patients with either local or distant recurrence will be removed from the study. Five-year survival rates and two-year recurrence rates will be the major objectives of this study.

#### PROGRESS

One patient was entered during FY 84 and was randomized to cystectomy alone. To this point she has tolerated the procedure well.

STATUS: (0)



**TITLE: SWOG 8219: Evaluation of Combined or Sequential  
Chemo-Endocrine Therapy in the Treatment of Advanced  
Adenocarcinoma of the Prostate, Phase III**

**PRINCIPAL INVESTIGATOR: MAJ Howard Davidson, MC**

**PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC James E. Congdon, MC  
LTC Irwin B. Dabe, MC  
MAJ Thomas M. Baker, MC  
MAJ Alfred H. Chan, MC  
MAJ Timothy J. O'Rourke, MC**

**WORK UNIT NO: 83/60**

#### TECHNICAL OBJECTIVE

To compare the efficacy of the sequential use of endocrine therapy followed at the time of progression by cytotoxic chemotherapy (Adriamycin and cyclophosphamide) versus the combination of endocrine therapy and chemotherapy in the treatment of advanced adenocarcinoma of the prostate by determination of the response rate, response duration, and duration of survival.

#### METHOD

Patients will be stratified as to the type of endocrine therapy (orchiectomy or diethylstilbestrol [DES]), performance status, and good risk or poor risk. Patients will be randomized to either Arm I (endocrine therapy followed at the time of progression by chemotherapy with cyclophosphamide and Adriamycin) or Arm II (endocrine therapy combined with cyclophosphamide and Adriamycin beginning two weeks after the orchiectomy or the initiation of DES). Endocrine therapy for both arms will consist of a bilateral orchiectomy or, if the patient refuses surgery, diethylstilbestrol. Courses will be repeated every 21 days. A minimum of two cycles will be considered an adequate trial. When a total of 300 mg/M<sup>2</sup> adriamycin in good risk or 200 mg/M<sup>2</sup> in poor risk patients has been given, it will be discontinued and cyclophosphamide will be given alone at a dose of 1000 mg/M<sup>2</sup> (good risk) or 750 mg/M<sup>2</sup> (poor risk) every three weeks. Cyclophosphamide will be discontinued in patients who are in complete or partial remission or who have stable disease after one year of chemotherapy. Patients with progressive disease after the sequential or combined chemo-endocrine therapy will be treated on another protocol.

#### PROGRESS

One patient has been entered at MAMC on the sequential arm. Groupwide, 76 patients have been entered; 14% with severe granulocytopenia in the arm with combined chemo-endocrine therapy.

**STATUS: (O)**

TITLE: SWOG 8218 - Evaluation of Spirogermanium (NSC-192965)  
in Renal Cell Carcinoma, Phase II

PRINCIPAL INVESTIGATOR: MAJ Howard Davidson, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC James E. Congdon, MC  
LTC Irwin B. Dabe, MC  
MAJ Thomas M. Baker, MC  
MAJ Alfred H. Chan, MC  
MAJ Timothy J. O'Rourke, MC

WORK UNIT NO: 83/54

#### TECHNICAL OBJECTIVES

To determine the response rate and remission of renal cell carcinoma when treated with spirogermanium used as a 60 minute infusion in a three times weekly schedule, and to define the qualitative and quantitative toxicities of spirogermanium administered in a Phase II study.

#### METHOD

Eligible patients will be treated at a dose of 80 mg/M<sup>2</sup>, IV, three times a week. The dosage will be slowly escalated with weekly increments of 10 mg/M<sup>2</sup> to a total of 120 mg/M<sup>2</sup>. The medicine will be continued on a three times a week basis until there is evidence of complete tumor remission or objective evidence of disease progression.

#### PROGRESS

(3/83 - 10/83) One patient entered at MAMC. On two occasions the patient developed phlebitis on side of administration of the spirogermanium. This resolved without sequelae.

STATUS: (C)

TITLE: SWOG 8217: Evaluation of Spirogermanium (NSC-192965) in  
Ademocarcinoma of the Prostate, Phase II

PRINCIPAL INVESTIGATOR: MAJ Howard Davidson, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC James E. Congdon, MC  
LTC Irwin B. Dabe, MC  
MAJ Thomas M. Baker, MC  
MAJ Alfred H. Chan, MC  
MAJ Timothy J. O'Rourke, MC

WORK UNIT #83/44

#### TECHNICAL OBJECTIVE

To determine the response rate and remission duration of adenocarcinoma of the prostate when treated with spirogermanium used as a 60 minute infusion in a three times weekly schedule, and to define the qualitative and quantitative toxicities of Spirogermanium administered in a Phase II study.

#### METHOD

Patients will receive a dose of spirogermanium based upon their body height and weight, given IV on an outpatient basis, three times a week. This treatment regimen will continue for a period of one year, until unusual side effects develop, or until evidence of objective disease progression is noted.

#### PROGRESS

No entries at MAMC during FY 84. One patient was entered in FY 83 and experienced lethargy and confusion; more likely due to underlying OBS than to the drug. The patient had progressive disease and was taken off study.

Groupwide, 27 patients have been entered. The most common toxicities were mild somnolence and nausea.

STATUS: (O)

TITLE: SWOG 8216/38 : Comparison of BCG Immunotherapy and  
Adriamycin for Superficial Bladder Cancer, Phase III

PRINCIPAL INVESTIGATOR: MAJ Howard Davidson, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC William D. Belville, MC  
LTC Irwin B. Dabe, MC  
MAJ Thomas M. Baker, MC  
MAJ Alfred H. Chan, MC  
MAJ Timothy J. O'Rourke, MC  
CPT Michael D. Stone, MC

WORK UNIT NO: 84/18

#### TECHNICAL OBJECTIVES

To compare the effectiveness of intravesical BCG immunotherapy with intravesical Adriamycin in chemotherapy with respect to disease-free interval and two-year recurrence rate; to compare the toxicity of topical immunotherapy and chemotherapy; and to obtain experience regarding disease-free interval and the recurrence rate in patients who develop tumor recurrence and are then crossed over to the alternative treatment arm.

#### METHOD

Following a standard transurethral resection, patients will be stratified by the presence or absence of documented carcinoma *in situ* and as to prior chemotherapy and then randomized to receive BCG immunotherapy or Adriamycin chemotherapy. Patients who develop tumor recurrence following treatment will be eligible for crossover to the other treatment arm.

#### PROGRESS

Three patients were entered at MAMC during FY 84. One patient developed flu-like reactions to BCG injections, ulcerative lesions, and possible systemic BCG infection. Groupwide data suggest a significantly better response to the BCG than the Adriamycin.

STATUS: (O)

TITLE: SWOG 8215: Comparison of Combination Chemotherapy with VP-16 and Cis-Platinum vs BCNU, Thiotepa, Vincristine, and Cyclophosphamide in Patients with Small Cell Carcinoma of the Lung Who Have Failed or Relapsed Primary Chemotherapy, Phase III

PRINCIPAL INVESTIGATOR: MAJ Thomas M. Baker, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC James E. Congdon, MC  
LTC Irwin B. Dabe, MC  
MAJ Alfred H. Chan, MC  
MAJ Howard Davidson, MC  
MAJ Manuel J. Martinez, MC  
MAJ Timothy J. O'Rourke, MC

WORK UNIT NO: 83/67

#### TECHNICAL OBJECTIVES

To confirm the efficacy of combination VP-16-213 (VP-16) and Cis-diamminedichloroptinum (Cis-platinum) in the treatment of patients with small cell carcinoma of the lung who have failed or relapsed on firstline treatment protocols; and through a randomized trial, to compare the remission rate, duration of remission and toxicity between the combination of VP-16 plus Cis-platinum and the combination of bis-chloroethylnitrosourea (BCNU), triethylenethiophosphoramide (Thiotepa), Vincristine (Oncovin), and Cyclophosphamide (Cytosan) in the same group of patients.

#### METHOD

Patients will be randomized to either one of two treatments.

Arm I (BCNU, Thiotepa, Vincristine, and Cyclophosphamide): Both good and poor risk patients will receive Vincristine, 2 mg, Thiotepa, 20 mg/M<sup>2</sup>, Cyclophosphamide, 500 mg/M<sup>2</sup>, and BCNU, 100 mg/M<sup>2</sup>, IV on days 1, 21, and 42. This therapy will be repeated every three weeks until progression of disease occurs.

Arm II (VP-16 and Cis-Platinum): Good risk patients will receive VP-16, 125 mg/M<sup>2</sup>, IV, days 1, 3, and 4 and Cis-Platinum 75 mg/M<sup>2</sup>, IV, day 2. For Poor risk patients, the dosages will be reduced to 100 mg/M<sup>2</sup> and 50 mg/M<sup>2</sup>. Chemotherapy with VP-16 and Cis-platinum will be repeated every four weeks until progression occurs.

#### PROGRESS

No entries at MAMC in FY 84. One patient was entered in FY 83 and expired after several weeks of therapy. No unexpected adverse reactions.

STATUS: (0)

TITLE: SWOG 8211: Evaluation of Cis-Diamminedichloroplatinum  
in Disseminated Gastric Adenocarcinoma, Phase II

PRINCIPAL INVESTIGATOR: MAJ Howard Davidson, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC James E. Congdon, MC  
LTC Irwin B. Dabe, MC  
MAJ Thomas M. Baker, MC  
MAJ Alfred H. Chan, MC  
MAJ Timothy J. O'Rourke, MC

WORK UNIT NO. 83/43

#### TECHNICAL OBJECTIVES

To test the response rate of cis-diamminedichloroplatinum (DDP) in patients with disseminated and measurable adenocarcinoma of the stomach who are previously untreated, and to test the response rate of DDP in patients with disseminated adenocarcinoma of the stomach who have previously been treated with 5-fluorouracil, Adriamycin, and mitomycin-C (5-FAM) chemotherapy.

#### METHOD

Patients will be admitted to the hospital on a once every three weeks basis for overnight chemotherapy infusion. DDP will be given in a dose based on the patient's body height and weight. Treatment will continue on a once every three weeks basis for a minimum of one year or until evidence of objective disease progression has been determined.

#### PROGRESS

(2/83 - 9/84) No patients entered at MAMC.

STATUS: (C)

TITLE: SWOG 8245: Combination Chemotherapy of Unfavorable  
Histology Non-Hodgkin's Lymphoma with CHOP and CVB  
(Alternating), Phase II.

PRINCIPAL INVESTIGATOR: MAJ Thomas M. Baker, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC Irwin B. Dabe, MC  
MAJ Alfred H. Chan, MC  
MAJ Howard Davidson, MC  
MAJ Timothy J. O'Rourke, MC  
CPT Michael D. Stone, MC

WORK UNIT NO: 84/20

#### TECHNICAL OBJECTIVES

To gain experience with a treatment program utilizing a combination of two alternating non-cross resistant drug regimens in the treatment of "poor prognosis" lymphomas and to determine an approximate complete remission rate to the cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP)/cis-platinum, vinblastine, and bleomycin (CVB) treatment program prior to initiating a group-wide Phase III study utilizing this program.

#### METHOD

Treatment will consist of five (5) seven-week courses of therapy. A course of therapy is composed of the administration of CHOP (days 1-21) and CVB (days 22-49). An adequate trial of treatment will be one course of therapy. Patients with documented progressive disease during therapy or less than a complete remission at the completion of the treatment will be removed from the study.

#### PROGRESS

(11/83 - 3/84) Two patients were entered at MAMC during FY 84 with no unexpected toxicity.

STATUS: (C)

TITLE: SWOG 8276: Evaluation of m-AMSA, VP-16-213 and  
5-Azacytidine Combination Chemotherapy in Adult Acute  
Non-Lymphocytic Leukemia, Phase II -Pilot

PRINCIPAL INVESTIGATOR: MAJ Howard Davidson, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC Irwin B. Dabe, MC  
MAJ Thomas M. Baker, MC  
MAJ Alfred H. Chan, MC  
MAJ Timothy J. O'Rourke, MC  
CPT Michael Stone, MC

WORK UNIT NO: 84/34

#### TECHNICAL OBJECTIVES

To determine the response rate and response duration of adult acute non-lymphocytic leukemia treated with a combination of m-AMSA, VP-16-213 and 5-azacytidine as induction therapy and to define the qualitative and quantitative toxicities of this regimen in a Phase II study in this population.

#### METHOD

Patients will be treated every 21 days until an A-1 marrow is achieved or until two courses have been completed. At the end of two full courses, if the bone marrow has shown improvement but the patient is still not in complete remission, two additional courses will be administered in an effort to achieve an A-1 status. After complete remission is demonstrated, the patients will be taken off of chemotherapy and followed on a monthly basis with repeat bone marrow aspirates to document the duration of complete remission.

#### PROGRESS

(2/84 - 9/84) No patients entered at MAMC. Groupwide, 29 patients were entered, but no data is available at this point.

STATUS: (C)



TITLE: SWOG 8278: FUVAC with Intensive Consolidation for  
ER-Metastatic Breast Cancer, Phase II, Pilot

PRINCIPAL INVESTIGATOR: COL Friedrich H. Stutz, MC

PROFESSIONAL ASSISTANTS: COL Donald H. Kull, MC  
MAJ Thomas Baker, MC  
MAJ Howard Davidson, MC

WORK UNIT NO: 84/36

#### TECHNICAL OBJECTIVES

To determine the feasibility and toxicity of combination chemotherapy induction, followed by consolidation therapy with sequential half-body irradiation or high-dose cyclophosphamide with total body irradiation and autologous bone marrow infusion, in patients with disseminated, estrogen receptor negative breast cancer; to determine complete and partial response rates; and to describe response duration and survival of patients treated with such a regimen.

#### METHOD

All patients will receive induction therapy of six courses of FUVAC chemotherapy. Following this, patients who are good risk and whose marrow is negative for tumor cells will receive consolidation therapy with cyclophosphamide and total body irradiation. Poor risk patients or those patients with the presence of tumor cells in the marrow will receive sequential hemibody irradiation only, beginning on week 18 of the study. Following this, no further therapy will be administered. Patients with progressive disease after one course of induction therapy or failure to achieve at least an objective or subjective improvement by the end of four induction courses will be removed from the study

#### PROGRESS

One patient was entered at MAMC in FY 84. She had progression on treatment and expired from disease.

STATUS: (0)

**TITLE: SWOG 8293: Intergroup Phase III Protocol for the Management of Locally or Regionally Recurrent but Surgically Resectable Breast Cancer**

**PRINCIPAL INVESTIGATOR: MAJ Howard Davidson, MC**

**PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC Irwin B. Dabe, MC  
MAJ Thomas M. Baker, MC  
MAJ Alfred H. Chan, MC  
MAJ Timothy J. O'Rourke, MC  
CPT Michael Stone, MC**

**WORK UNIT NO: 84/47**

#### TECHNICAL OBJECTIVES

To better define the relative roles of systemic and local treatments in the care of resectable locally or regionally recurrent cancer of the breast in patients who have no evidence of disease after resection; to assess the effects of chemotherapy and radiation therapy (singly or in combination) administered immediately after surgical resection on local control, disease-free interval, and pattern of re-recurrence; to determine the effect of the administration of systemic chemotherapy or radiation therapy, which has been delayed until local, regional, re-recurrence, on local and regional control, disease-free survival, patterns of relapse, and survival; and to determine the influence of disease-free interval, size, and extent of local or regional recurrence on the effectiveness of treatment with chemotherapy and radiation therapy (singly or in combination).

#### METHOD

After patients with technically resectable loco-regional recurrent breast cancer have been rendered clinically free of disease (NED) by surgical resection and appropriate staging, they will be allocated to Schema A, B, or C. Patients allocated to Schema A will receive nine cycles of chemotherapy. Upon completion of drug therapy, these patients will be restaged and if found NED will proceed to observation or to consolidation radiation therapy. Patients allocated to Schema B will initially be randomized to receive radiation therapy followed by observation or to nine cycles of chemotherapy followed by consolidation radiation therapy. Patients allocated to Schema C will receive initially either radiation therapy or chemotherapy. Those who receive radiation therapy will be observed without further treatment. Those who receive chemotherapy and who are found NED after restaging after 9 cycles of treatment will receive consolidation radiation therapy or observation without further treatment.

Regardless of initial treatment, patients will be followed for local and/or distant re-recurrence. Patients who experience local re-recurrence during active induction chemotherapy (Arms I and II) will come off study. Patients who experience local re-recurrence during primary radiation therapy (Arm III) will have radiation therapy terminated, the re-recurrence excised if technically feasible, and then given nine cycles of chemotherapy. Patients who develop local re-recurrence during consolidation radiation therapy (Arm I) will come off study and will be followed for survival. Patients who develop local re-recurrence during the observation phase of Treatment Arms II and III will remain on study and will be treated per schema. Patients who develop distant recurrence will come off study and will be followed for survival.

PROGRESS

No entries at MAMC.

STATUS: (0)

**TITLE:** SWOG 8294 - Evaluation of Adjuvant Therapy and Biological Parameters in Node Negative Operable Female Breast Cancer (ECOG, EST-1180), Intergroup Study

**PRINCIPAL INVESTIGATOR:** MAJ Howard Davidson, MC

**PROFESSIONAL ASSISTANTS:** COL Friedrich H. Stutz, MC  
LTC James E. Congdon, MC  
LTC Irwin B. Dabe, MC  
MAJ Thomas M. Baker, MC  
MAJ Alfred H. Chan, MC  
MAJ Timothy J. O'Rourke, MC

**WORK UNIT NO:** 83/56

#### TECHNICAL OBJECTIVES

To assess the impact of short-term intensive chemotherapy with CMF to prevent disease recurrence and prolong survival in node negative patients with any size estrogen receptor negative tumors and node negative patients with estrogen receptor positive tumors whose pathological size is greater  $>3$  cm; to assess the impact of surgical procedure, estrogen receptor status, menopausal status and tumor size; to develop guidelines referable to hispathological features of node negative tumors which are reporducible and to assess their prognostic impact for disease-free survival and survival; to assess the value to CEA in predicting recurrence and survival rates; to assess the natural history of a subgroup with node negative, estrogen receptor positive small tumors (3 cm).

#### METHOD

Patients will have laboratory evaluations to ensure that there is no evidence of disseminated disease. They will be stratified into a number of treatment groups based on the site of tumor, estrogen receptor status, age, and menopausal status. Patients with primary tumors less than 3 cms in diameter who are estrogen receptor positive will be followed by close observation only to determine the natural history of their tumor. All other patients who have a somewhat greater likelihood of relapse will be randomized to receive either close observation only or 6 cycles of systemic chemotherapy. The chemotherapy will consist of 4 agents: cyclophosphamide, methotrexate, 5-fluorouracil, and prednisone given for six 28 day cycles. The dosage of the individual agents will be determined by body height and weight.

#### PROGRESS

Three patients were entered at MAMC in FY 84 for a total of four entries. Only mild side effects have been noted.

**STATUS:** (O)

**TITLE:** SWOG 8302: Phase II Study of Doxorubicin, Mitomycin-C,  
and 5-Fluorouracil in the Treatment of Metastatic  
Adenocarcinoma of the Prostate, Phase II

**PRINCIPAL INVESTIGATOR:** MAJ Thomas Baker, MC

**PROFESSIONAL ASSISTANTS:** COL Friedrich H. Stutz, MC  
LTC Irwin B. Dabe, MC  
MAJ Howard Davidson, MC  
MAJ Timothy J. O'Rourke, MC  
CPT Michael D. Stone, MC

**WORK UNIT NO:** 84/58

#### TECHNICAL OBJECTIVE

To test the effectiveness and toxicity of DMF (doxorubicin, mitomycin-C, and 5-fluorouracil) in the treatment of Stage D<sub>2</sub> adenocarcinoma of the prostate.

#### METHOD

Patients will be stratified as good risk or poor risk. Doxorubicin will be given on days 1 and 29, mitomycin-C will be given on day 1, and 5-FU will be given on days 1, 2, 29, and 30. Courses will be repeated at eight week intervals unless progression of disease occurs, at which time the patient will be removed from the study. An adequate trial will be defined as four weeks of treatment.

#### PROGRESS

(4/84 - 9/84) One patient was entered at MAMC. The patient had marked thrombocytopenia, bleeding gums, and petechia, which required platelet transfusion. In this patient and groupwide over all leukopenia, thrombocytopenia, and nausea and vomiting have been moderate to severe.

**STATUS:** (C)

TITLE: SWOG 8303: Evaluation of 2'Deoxycoformycin in Refractory Multiple Myeloma, Phase II

PRINCIPAL INVESTIGATOR: LTC Irwin Dabe, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
MAJ Thomas M. Baker, MC  
MAJ Alfred H. Chan, MC  
MAJ Howard Davidson, MC  
MAJ Timothy J. O'Rourke, MC  
CPT Michael Stone, MC

WORK UNIT NO: 84/49

#### TECHNICAL OBJECTIVES

To determine the response rate and response duration of refractory multiple myeloma treated with low dose 2'deoxycoformycin used in a single dose, every two week schedule, and to define the qualitative and quantitative toxicities of 2'deoxycoformycin administered in a Phase II Study.

#### METHOD

After vigorous hydration, an initial dose of 2'deoxycoformycin (4 mg/M<sup>2</sup>) will be given on day 1 and repeated every 14 days. PO fluids will be given days 1-5 of the cycle of therapy. Each patient will receive three courses of therapy to be considered evaluable for response. If no response is observed after three courses or there has been less than a 25% tumor reduction after four courses of treatment, patient will be removed from the study.

#### PROGRESS

One patient was entered at MAMC in FY 84. No adverse reactions were noted.

STATUS: (0)

TITLE: SWOG 8304: Phase II Evaluation of L-Alanosine in  
Metastatic Carcinoma of the Breast

PRINCIPAL INVESTIGATOR: MAJ Thomas M. Baker, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC Irwin B. Dabe, MC  
MAJ Alfred H. Chan, MC  
MAJ Howard Davidson, MC  
MAJ Timothy J. O'Rourke, MC  
CPT Michael D. Stone, MC

WORK UNIT NO: 83/73

#### TECHNICAL OBJECTIVES

To determine the antitumor activity as determined by response rate and duration of response of L-alanosine used on a three day, every three week schedule in patients with metastatic carcinoma of the breast who have failed on standard therapy and to determine the nature and degree of toxicity of L-alanosine.

#### METHOD

Patients will be stratified as to prior chemotherapy (minimal or extensive). L-alanosine will be given at a dose of 250 mg/M<sup>2</sup>/day. Courses of therapy will be repeated at three week intervals. An adequate trial of therapy is defined as two courses of therapy (six weeks) with follow-up tumor measurement or progression after one course of therapy. Therapy will be continued until progression of disease, relapse after attainment of remission, or unacceptable toxicity.

#### PROGRESS

(8/83 - 5/84) Two patients were entered at MAMC in FY 84. Groupwide, 35 patients were entered. Mild to moderate somnolence, diarrhea, nausea, chills, fever, and mucositis were seen overall; 25% had severe hypotension.

STATUS: (C)

TITLE: SWOG 8308: Combination Cis-Platinum and Dichloromethotrexate in Patients with Advanced Bladder Cancer, Phase II

PRINCIPAL INVESTIGATOR: MAJ Howard Davidson, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC Irwin B. Dabe, MC  
MAJ Thomas M. Baker, MC  
MAJ Timothy J. O'Rourke, MC  
CPT Michael Stone, MC

WORK UNIT NO: 84/78

#### TECHNICAL OBJECTIVES

To obtain data regarding the activity and toxicity of combination cis-platinum and dichloromethotrexate in patients with objectively measurable metastatic transitional cell carcinoma of the bladder who have good renal function and who have not previously received chemotherapy and to investigate the single agent activity and toxicity of dichloromethotrexate in previously untreated patients with impaired renal function.

#### METHOD

Patients with measurable metastatic disease, adequate hepatic and cardiac function, adequate bone marrow reserve, and no prior systemic chemotherapy will be eligible. Patients who have impaired renal function will receive dichloromethotrexate alone; patients with good renal function will receive dichloromethotrexate and cis-platinum. Cis-platinum will be given 70 mg/M<sup>2</sup>, the first and the fifth week with normal saline hydration, pre and post. Dichloromethotrexate will be given once weekly on an escalating dose schedule, starting at 400 mg/M<sup>2</sup> in good risk patients and 300 mg/M<sup>2</sup> in poor risk patients. After eight weeks of treatment, there will be a three week rest period; non-responding patients will be taken off study and responding patients will go to a less intensive maintenance phase.

#### PROGRESS

No entries at MAMC in Fy 84.

STATUS: (O)



TITLE: SWOG 8312, Megestrol Acetate and Aminoglutethimide/  
Hydrocortisone in Sequence or in Combination as Second-Line  
Endocrine Therapy of Estrogen Receptor Positive Metastatic  
Breast Cancer, Phase III

PRINCIPAL INVESTIGATOR: MAJ Thomas M. Baker, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC Irwin B. Dabe, MC  
MAJ Howard Davidson, MC  
MAJ Timothy J. O'Rourke, MC  
CPT Michael D. Stone, MC

WORK UNIT NO: 84/72

#### TECHNICAL OBJECTIVES

To determine whether combination hormonal therapy with aminoglutethimide and hydrocortisone plus megestrol acetate, agents thought to have different mechanisms of action, offers an improved response rate with prolonged response duration and increased patient survival over the sequential use of each agent in estrogen receptor positive patients who have progressed after responding to primary hormonal treatment with tamoxifen; to assess the relative toxicities of megestrol acetate and medical adrenalectomy; and to assess the value of progesterone receptors in predicting subsequent responses to a variety of hormonal therapies.

#### METHOD

Patients will be randomized after documented disease progression on tamoxifen to: Arm I - megestrol acetate, 40 mg p.o., 4 times daily given alone until there is documented evidence of disease progression; Arm II - aminoglutethimide, 250 mg p.o., twice daily for two weeks, then 250 mg p.o. four times daily plus hydrocortisone, 20 mg p.o. upon rising, 20 mg p.o. at 1700 hrs, and 60 mg p.o. at bedtime, daily for two weeks, then 10 mg p.o. upon rising, 10 mg p.o. at 1700 hrs, and 20 mg p.o. at bedtime; or Arm III - megestrol acetate as in Arm I plus aminoglutethimide as in Arm II plus hydrocortisone as in Arm II. An adequate trial of each arm will consist of at least eight weeks of daily therapy, in the absence of documented evidence of disease progression. Patients in Arms I and II with documented progressive disease after an adequate trial will be crossed over to the other treatment arm. The only exception to crossover will be patients who develop life threatening brain, liver, or pulmonary metastases who require systemic chemotherapy. Patients randomized to Arm III will go off study at the time of disease progression.

#### PROGRESS

No entries at MAMC.

STATUS: (O)

TITLE: SWOG 8313: Multiple Drug Adjuvant Chemotherapy for  
Patients with ER Negative Stage II Carcinoma of Breast,  
Phase III

PRINCIPAL INVESTIGATOR: MAJ Howard Davidson, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC Irwin B. Dabe, MC  
MAJ Thomas Baker, MC  
MAJ Timothy J. O'Rourke, MC  
CPT Michael D. Stone, MC

WORK UNIT NO: 84/59

#### TECHNICAL OBJECTIVES

To compare through a randomized prospective study the recurrence rates and disease-free intervals for postoperative axillary node positive estrogen receptor negative breast cancer patients given adjuvant therapy with either short term intense chemotherapy (FAC-M) or one year standard chemotherapy (CMFVP); to compare the effect of these two adjuvant therapies on survival; and to compare the relative toxicity of the two therapies.

#### METHOD

Women who have histologically proven breast cancer with axillary lymph node metastasis and negative estrogen receptors will be entered 14-21 days post-lumpectomy or within 14-42 days post-mastectomy. They will be randomly allocated to receive either:

Arm I - a tapering course of oral prednisone for 6 weeks, weekly IV vincristine for 10 weeks, weekly IV methotrexate, and weekly IV 5-FU plus daily oral cyclophosphamide for a total of one year.

or:

Arm II - four cycles of adriamycin (IV day 1), cyclophosphamide (IV day 1), 5-FU (IV days 1 and 8), and methotrexate (IV day 22). Each cycle will be five weeks and total duration of therapy in this arm is approximately 20 weeks.

Added to this protocol will be a sub-study to determine the prognostic significance of circulating human mammary epithelial antigens. This will involve blood tests prior to chemotherapy and then once every three months.

#### PROGRESS

No entries at MAMC.

STATUS: (O)

TITLE: SWOG 8316: Evaluation of Fludarabine Phosphate  
(NSC-312887) in Renal Cell Carcinoma, Phase II

PRINCIPAL INVESTIGATOR: MAJ Thomas Baker, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
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MAJ Timothy J. O'Rourke, MC  
CPT Michael D. Stone, MC

WORK UNIT NO: 84/60

#### TECHNICAL OBJECTIVES

To determine the response rate and remission duration of renal cell carcinoma when treated with fludarabine phosphate and to define the qualitative and quantitative toxicities of fludarabine phosphate administered in a Phase II study.

#### METHOD

Fludarabine phosphate, 25 mg/M<sup>2</sup>, will be given IV daily for five consecutive days and repeated every 28 days. Patients showing a complete or partial response will continue to receive therapy until disease relapse or until they have received therapy for one year after achieving a complete remission. Patients with progressive disease or relapse after two courses of therapy will have therapy with fludarabine phosphate discontinued.

#### PROGRESS

One patient entered at MAMC in FY 84 with no adverse effects; too early for evaluation of response.

STATUS: (O)

TITLE: SWOG 8367: Combined Modality Treatment of Regional  
Non-Small Cell Lung Cancer, Phase I-II Pilot

PRINCIPAL INVESTIGATOR: MAJ Howard Davidson, MC

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WORK UNIT NO: 84/61

#### TECHNICAL OBJECTIVES

To determine the feasibility and acute toxicity of a sequential approach with combination chemotherapy and neutron-based radiation therapy in the treatment of regional (limited, unresectable) non-small cell lung carcinoma; to determine complete and partial response rates and response duration with such a program, and to assess survival and long-term side effects in this treated population.

#### METHOD

Patients will receive outpatient vinblastine and mitomycin-C followed three weeks later by inpatient vinblastine and cis-platinum. Following three weeks rest, neutron radiation therapy to the chest and photon therapy to the brain (prophylaxis) will be given. Upon completion of radiation therapy (week 14), two additional cycles of VeMi/VeP will be given. Upon completion of chemotherapy, no further therapy will be administered and the patient will be followed.

#### PROGRESS

No entries at MAMC.

STATUS: (O)

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## APPENDIX II

### Recommendations from the Declaration of Helsinki

#### I. Basic Principles

1. Clinical research must conform to the moral and scientific principles that justify medical research and should be based on laboratory and animal experiments or other scientifically established facts.

2. Clinical research should be conducted only by scientifically qualified persons and under the supervision of a qualified medical man.

3. Clinical research cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

4. Every clinical research project should be preceded by careful assessment of inherent risks in comparison to foreseeable benefits to the subject or to others.

5. Special caution should be exercised by the doctor in performing clinical research in which the personality of the subject is liable to be altered by drugs or experimental procedure.

#### II. Clinical Research Combined with Professional Care

1. In the treatment of the sick person, the doctor must be free to use a new therapeutic measure, if in his judgment it offers hope of saving life, reestablishing health, or alleviating suffering.

If at all possible, consistent with patient psychology, the doctor should obtain the patient's freely given consent after the patient has been given a full explanation. In case of legal incapacity, consent should also be procured from the legal guardian; in case of physical incapacity, the permission of the legal guardian replaces that of the patient.

2. The nature, the purpose, and the risk of clinical research must be explained to the subject by the doctor.

3. a. Clinical research on a human being cannot be undertaken without his free consent after he has been informed; if he is legally incompetent, the consent of the legal guardian should be procured.

b. The subject of clinical research should be in such a mental, physical, and legal state as to be able to exercise fully his power of choice.

## APPENDIX I

### GUIDING PRINCIPLES OF THE CARE AND USE OF ANIMALS

Approved by the  
Council of the American Physiological Society

Only animals that are lawfully acquired shall be used in this laboratory, and their retention and use shall be in every case in strict compliance with state and local laws and regulations.

Animals in the laboratory must receive every consideration for their bodily comfort; they must be kindly treated, properly fed, and their surroundings kept in a sanitary condition.

Appropriate anesthetics must be used to eliminate sensibility to pain during operative procedures. Where recovery from anesthesia is necessary during the study, acceptable technic to minimize pain must be followed. Curarizing agents are not anesthetics. Where the study does not require recovery from anesthesia, the animal must be killed in a humane manner at the conclusion of the observations.

The postoperative care of animals shall be such as to minimize discomfort and pain and in any case shall be equivalent to accepted practices in schools of veterinary medicine.

When animals are used by students for their education or the advancement of science, such work shall be under the direct supervision of an experienced teacher or investigator. The rules for the care of such animals must be the same as for animals used for research.

TITLE: SWOG 8490: Phase II Study of PAC (Cis-Platinum, Adriamycin, and Cyclophosphamide) in Treatment of Invasive Thymoma, Intergroup Study

PRINCIPAL INVESTIGATOR: MAJ Thomas M. Baker, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC Irwin B. Dabe, MC  
MAJ Howard Davidson, MC  
MAJ Timothy J. O'Rourke, MC  
CPT David Bryson, MC  
CPT Michael Stone, MC

WORK UNIT NO: 84/79

#### TECHNICAL OBJECTIVES

To determine the objective response rate in extensive and limited invasive thymoma treated with PAC and to determine the duration of remission of patients with limited invasive thymoma treated with split course radiotherapy plus PAC and patients with extensive disease treated with PAC alone.

#### METHOD

Patients will receive PAC on day 1 every three weeks. After two courses of PAC, patients will be evaluated. Non-responders will go off study. Responders with limited disease will receive split course radiotherapy to be given in weeks 7 and 8 and in week 12 followed four weeks later by six additional courses of PAC. Responders with extensive disease or limited disease with prior chest radiotherapy will receive six additional courses of PAC at three week intervals.

#### PROGRESS

No entries at MAMC.

STATUS: (O)

TITLE: SWOG 8386: Evaluation of Fludarabine Phosphate in Colorectal Carcinoma, Phase II

PRINCIPAL INVESTIGATOR: MAJ Thomas M. Baker, MC

PROFESSIONAL ASSISTANTS: COL Friedrich Stutz, MC  
LTC Irwin Dabe, MC  
MAJ Alfred Chan, MC  
MAJ Howard Davidson, MC  
MAJ Timothy O'Rourke, MC  
CPT Michael Stone, MC

WORK UNIT NO: 84/48

#### TECHNICAL OBJECTIVES

To determine the antitumor activity of fludarabine phosphate in patients with colorectal carcinoma by determination of the response rate and remission duration and to further define the qualitative and quantitative toxicities of this drug in a Phase II study.

#### METHOD

Courses of fludarabine phosphate will be administered for five days every 28 days. Patients showing a complete response or partial response will continue to receive therapy until disease relapse or until they have received therapy for one year after achieving a complete remission. Patients with progressive disease after two courses of therapy or relapse will have therapy with fludarabine phosphate discontinued.

#### PROGRESS

(4/84 - 9/84) Two patients were entered at MAMC. One patient developed total body rash which subsided when given benadryl and prednisone taper. The other patient died six hours after second course but death thought not to be due to chemotherapy but due to progressive cancer.

STATUS: (C)



TITLE: SWOG 8378: Evaluation of Fludarabine Phosphate in  
Chronic Lymphocytic Leukemia

PRINCIPAL INVESTIGATOR: MAJ Thomas M. Baker, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC Irwin B. Dabe, MC  
MAJ Alfred H. Chan, MC  
MAJ Howard Davidson, MC  
MAJ Timothy J. O'Rourke, MC  
CPT Michael Stone, MC

WORK UNIT NO: 84/37

#### TECHNICAL OBJECTIVES

To determine the response rate and remission duration of relapsing or refractory chronic lymphocytic leukemia treated with fludarabine phosphate used in a daily times five, every four week schedule and to define qualitative and quantitative toxicities of fludarabine phosphate in a Phase II study in this population.

#### METHOD

To achieve maximum tolerated lymphotoxicity, the initial dose will be escalated in increments not to exceed 25% as a maximum of five patients are accrued to the initial dose and the toxicity of fludarabine phosphate is evaluated. The initial dose will be 20 mg/M<sup>2</sup> daily for five days to be administered as a rapid IV infusion and repeated every 28 days. Patients will receive an initial three courses of fludarabine phosphate. If there is evidence of progression of disease, treatment will be discontinued and the patient will be taken off the study. If there is evidence of response, the patient will receive three more courses for a total of six courses of therapy. Patients will then be re-evaluated and categorized as either responders or non-responders. Patients achieving a complete response will be followed without further therapy to disease relapse. Patients achieving a partial response after six courses of fludarabine phosphate will receive six additional courses at which time they will be reclassified as complete response or partial response. Patients remaining in partial response will be taken off study and patients in complete remission will be followed to disease relapse.

#### PROGRESS

No entries at MAMC.

STATUS: (0)

TITLE: SWOG 8370: Vinblastine and Cis-Platinum in the Treatment  
of Refractory Sarcomas, Phase II - Pilot

PRINCIPAL INVESTIGATOR: MAJ Howard Davidson, MC

PROFESSIONAL ASSISTANTS: COL Friedrich H. Stutz, MC  
LTC Irwin B. Dabe, MC  
MAJ Thomas M. Baker, MC  
MAJ Alfred H. Chan, MC  
MAJ Timothy J. O'Rourke, MC  
CPT Michael Stone, MC

WORK UNIT NO: 84/07

#### TECHNICAL OBJECTIVE

To evaluate the response rate of refractory soft tissue sarcoma  
to the drug combination of vinblastine and cis-platinum.

#### METHOD

This is a prospective, one arm pilot study for the treatment of  
measurable, refractory (to standard therapy) sarcomas. Cis-  
Platinum is given on day 1 after appropriate hydration, followed  
by a 5 day continuous infusion of vinblastine. The treatment  
will continue for as long as it can be tolerated and controls  
the disease (stable disease or response).

#### PROGRESS

No entries at MAMC.

STATUS: (O)

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